Expanding the Scope of Regioselective Hydroformylation Using Catalytic Scaffolding Ligands

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a thesis

by

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submitted in partial fulfillment of the requirements

for the degree of

Master of Science

October 2009

EXPANDING THE SCOPE OF REGIOSELECTIVE HYDROFORMYLATION USING CATALYTIC SCAFFOLDING LIGANDS

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Abstract. General and efficient methods for the selective hydroformylation of allylic alcohols and amines utilizing a directing group approach.

Chapter One: A brief overview of directing group strategies in organic synthesis including a description of the design of a new class of ligands.

Chapter Two: Expanding the substrate scope of scaffolding ligand directed hydroformylation to encompass allylic sulfonamides.

Chapter Three: Preliminary studies towards the scaffolding ligand directed hydroformylation to include 1,1-disubstituted secondary alcohols. Includes catalytic examples of diastereoselective hydroformylation.

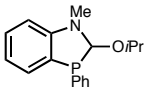
Acknowledgements

I would like to thank Dr. Kian Tan for teaching and training me and for allowing me to grow as a researcher. I would also like to thank Dr. T. Ross Kelly and Dr. Lawrence Scott for reading and critiquing this work. I thank Kwame Frimpong, Nicholas McBride, Kelly Mullen, Kristine Frank and Amanda Worthy for their assistance in reviewing this work.

List of Abbreviations

Ac	acetate
Ar	aryl
Bu	*n*-butyl
Convn	conversion
DG	directing group
DMF	*N,N*-dimethylformamide
eq	equation
equiv	equivalent
EtOAc	ethyl acetate
FG	functional group
GC	gas chromatography
h	hours
H_2	hydrogen gas
$HC(OMe)_3$	trimethylorthoformate
HRMS	high resolution mass spectrometry
*i*Pr	*iso*-propyl
IR	infrared
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
min	minutes

NMR	nuclear magnetic resonance
o-DPPB	*ortho*-diphenylphosphanylbenzoate
Ph	phenyl
PCC	pyridinium chlorochromate
PhH	benzene
psi	pounds per square inch
*p*TsOH	*para*-toluenesulfonic acid
SFC	super critical fluid chromatrography
SiO_2	silica
t-BuOOH	*tert*-butylperoxide
THF	tetrahydrofuran
UV	ultraviolet
Zn	zinc



For ease and convenience, the frequently used scaffolding ligand above will be referred to as Ligand I for the duration of this thesis

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Financial support was generously provided by Boston College. We are grateful to Dr. John Boylan for valuable assistance in the use and maintenance of the NMR facility; Mr. Marek Domin for his help in acquiring mass spectrometry; and Dr. Bo Li for his expertise in acquiring and interpreting X-ray structures. The Boston College Mass Spectrometry Facility is supported by the NSF (grant DBI-0619576). The X-ray facility at Boston College is supported by Schering-Plough.

Chapter 1: Use of Directing Group Strategies in Organic Synthesis

I. Introduction

The control of regio- and stereoselectivity is a paramount goal in organic synthesis. Although many strategies have been employed for this task, one of the most reliable and predictable has been the application of directing groups (DGs).[1] Directing groups have been used in a range of transformations including epoxidation, cyclopropanation, C-H functionalization, and hydroformylation.[1a] In some cases the DG is a common organic functionality, such as an alcohol, present within the substrate that leads to selective reaction (Section II). In others the DG is a less useful functional group that instead is an ideal ligand for a metal catalyst (Section III). In the latter cases, these DGs must be installed and removed in separate steps but often lead to highly efficient and selective reaction. It is worth considering that:

> "A transition metal catalyzed reaction that is effectively influenced by an internal heteroatom can be developed to reach regio- and stereoselectivity levels often attained with natural enzymes, but with the added bonus that the man-made catalyst enjoys much wider substrate compatibility."[1a]

Most interesting, is the expanding use of catalytic DGs that seek to take advantage of the best of both worlds (Section V) and the design of these new ligands (Section IV).

II. Classic Examples of Useful Functional Groups as Directing Groups

One of the oldest examples of a directed reaction was described for the Simmons-

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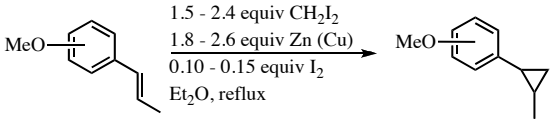
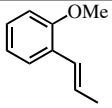
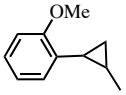
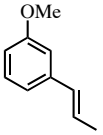
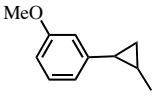
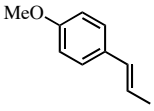
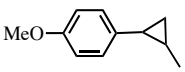
[1](a) Hoveyda, A.; Evans, D.; Fu, G. *Chem. Rev.* **1993**, *93,* 1307-1370. (b) Itami, K.; Yoshida, J. *Synlett.* **2006**, *2,* 157-180. (c) Oestreich, M. *Eur. J. Org. Chem.* **2005**, *5,* 783-792. (d) Kakiuchi, F.; Chatani, N. *Adv. Syn. Catal.* **2003**, *345,* 1077-1101. (e) Dick, A.; Sanford, M. *Tetrahedron.* **2006**, *62,* 2439-2463.

Smith cyclopropanation.[2] After the discovery of this zinc catalyzed process in 1958, the researchers expanded upon their work by testing the substrate scope of the reaction. In this study they made an important observation that not only did steric effects play a role in reactivity, but that coordination of an attached hydroxyl will "assist and direct addition" in the zinc-mediated cyclopropanation.[3] This observation comes from the comparison of reactivity between three constitutional isomers: *ortho*-, *meta*-, and *para*-methoxyphenylpropene (Table 1). The reactivity of the *ortho*-substituted substrate is higher than the other isomers, producing higher yields in a shorter amount of time. The proposed mode of direction is shown in Scheme 1, where the active zinc species coordinates to the oxygen DG.

Table 1. Examination of Constitutional Isomers in the Simmons-Smith Cyclopropanation

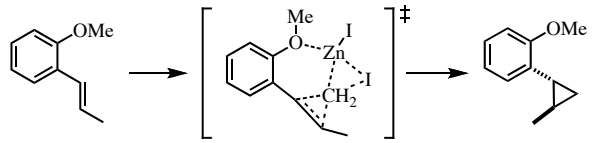


1.1 1.2

Olefin	Equiv. Zn (Cu)	Reaction Time (h)	Product	Yield (%)
	1.94	48		70
	1.75	48		60
	2.59	72		63

[2] Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958,** *80,* 5323-5324.
[3] Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959,** *81,* 4256-4264.

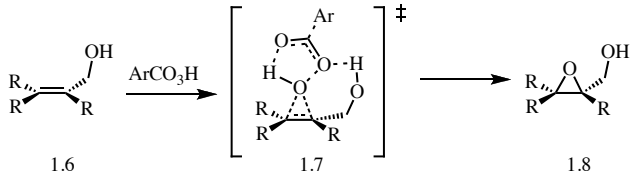
Scheme 1. Hydroxyl Assisted Cyclopropanation of a Benzylic Olefin



1.3 1.4 1.5

The discovery of an oxygen-directed process by Simmons and Smith occurred in the same time period as the realization of hydroxyl-directed epoxidation by Henbest and Wilson in 1959.[4] This team observed that the reaction of cyclic allylic alcohols with perbenzoic acid resulted in a strong diastereomeric preference, forming the epoxide predominantly syn to the hydroxyl group. The mechanism was postulated to be similar to the "butterfly" mechanism proposed by Barlett[5] in 1950 (Scheme 2).

Scheme 2. Butterfly Transition State in the Epoxidation of Olefins

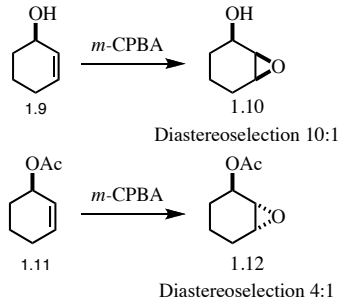


1.6 1.7 1.8

This mechanism was supported by the fact that protecting the hydroxyl group with an acetate group, thereby removing the potential hydrogen-bond donor, affords the opposite selectivity (Scheme 3).

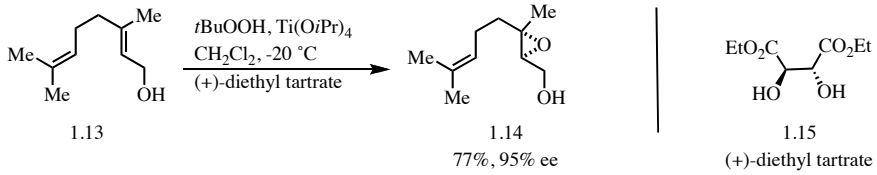
[4] Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1959,** 4136-4138.
[5] Bartlett, P. D. *Rec. Prog. Chem.* **1950,** *11,* 47-51.

Scheme 3. Effect of Acetate Protecting Group on Selectivity in Epoxidation



Hydroxyl-directed epoxidation has since seen vast improvements, leading to asymmetric variants including the well-known Sharpless Asymmetric Epoxidation exemplified by the reaction shown in Scheme 4.[6]

Scheme 4. Sharpless Asymmetric Epoxidation

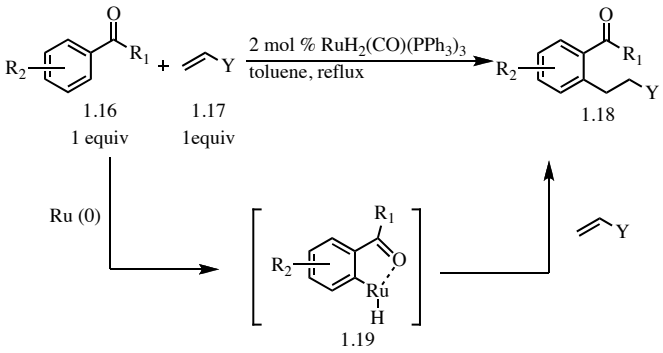


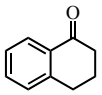
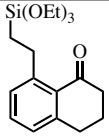
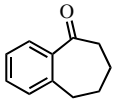
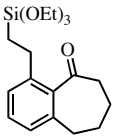
One of the first catalytic carbon-hydrogen bond activation reactions of unactivated substrates utilized a directing group strategy. A ketone binds to the ruthenium catalyst, putting the metal in proximity to the *ortho* C-H bond and allowing for a more facile and site-selective bond cleavage to give a cyclometallated intermediate. The metal is now poised for insertion into an olefin coupling partner, followed by reductive elimination to afford the observed product. "The importance of chelation is further demonstrated by the slower reaction of [Table 2, entry 1] compared to [Table 2, entry 2]; the latter involves a cyclometallated intermediate which is almost free from angle strain. Indeed, a corresponding five-memebered ketone, 1-indanone (not shown),

[6] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980,** *102,* 5974-5978.

which should produce greater ring strain in the cyclometallated intermediate, did not react at all."[7]

Table 2. *Ortho*- C-H Activation



Entry	Substrate	Product	Yield (%)
1			100
2			88

III. Removable Directing Groups

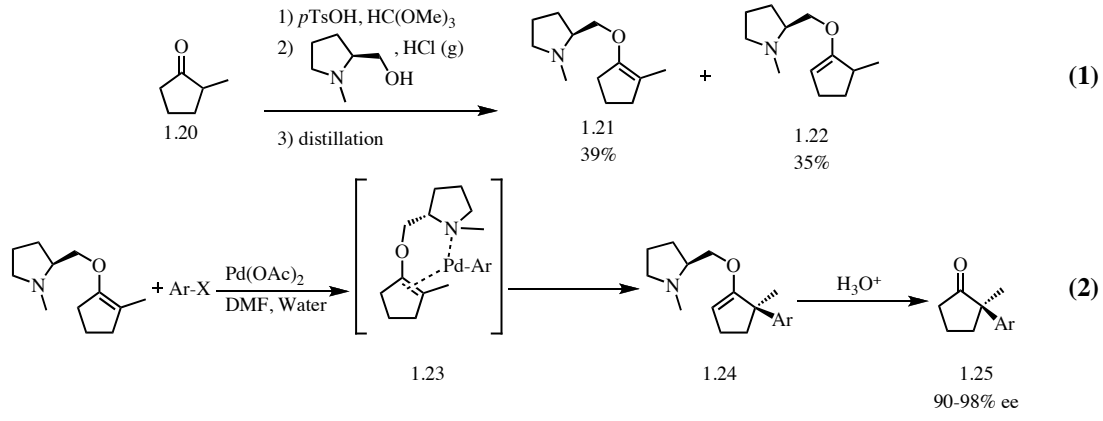
Unfortunately, the ideal ligand for a metal catalyst is not always a useful functional group handle as seen in the examples in section II. A common strategy to combat this fact is the use DGs that are built into the substrate.[8] This strategy, however, relies on the DG being incorporated into the substrate, and often requires the use of

[7] Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature.* **1993,** *366,* 529-531.
[8] Some representative examples can be found in: (a) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005,** *7,* 4149-4152. and the references therein; (b) Jackson, W. R.; Perlmutter, P.; Suh, G. *J. Chem. Soc., Chem. Commun.,* **1987,** 724-725.

functionalities that are difficult to remove. Researchers in this field have developed a number of removable DGs and described their use in several reactions, including the Heck reaction, C-H functionalization,[9] and hydroformylation.

An example of an effective removable group is shown in the case of the Heck reaction. This report was one of the first to accomplish an asymmetrical intermolecular Heck reaction to form a quaternary center through the employment of a chelation controlled pathway.[10] An inexpensive and commercially available amino alcohol was utilized as the chiral metal-coordinating auxillary, allowing this process to be suitable for commercial use. *(S)*-1-methyl-2-pyrrolidine-methanol was selected as the ideal auxillary and was smoothly incorporated through an acid-catalyzed acetalization-elimination protocol (Scheme 5, eq. 1). Once installed, the auxillary presumably forms a chelated structure (Scheme 5, eq. 2) that directs regioselectivity as well as enantioselectivity. A simple hydrolysis produces moderate two-step yields (50-80%) and excellent enantioselectivity (90-98% ee). As with many DG approaches, the installation and removal of the auxillary is the major drawback.

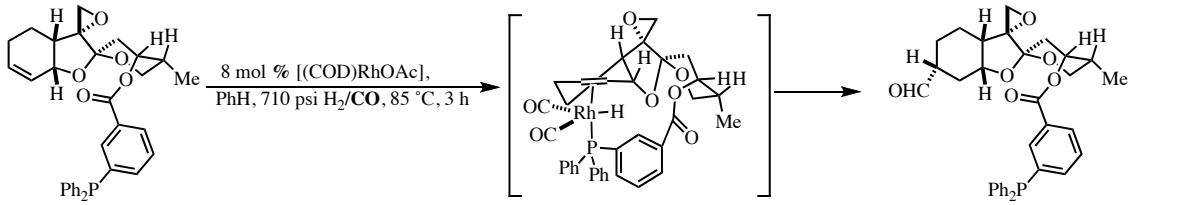
Scheme 5. Asymmetric Heck Reaction



[9] Jun, C.; Hong, J.; Kim, Y.; Chung, K. *Angew. Chem. Int. Ed.* **2000,** *39,* 3440-3442.
[10] Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2003,** *125,* 3430-3431.

A number of strategies involving different phosphine-based ligands have been applied to the directed hydroformylation of olefins. The first reported example of a DG approach in hydroformylation came in the empirically derived hydroformylation of a key intermediate in the total synthesis of (+)-Phyllanthocin.[11] Upon incorporation of a phosphine ligand into the substrate, the researchers observed increased reactivity as well as a cleaner reaction through a proposed intramolecular chelation (Scheme 6). To test this hypothesis, researchers oxidized the phosphine ligand. With the internal ligand no longer accessible, hydroformylation proceeded with poor regioselectivity providing a mixture with the undesired C4β-formyl product in 49% yield.

Scheme 6. Key Step in the Total Synthesis of (+)-Phyllanthocin



1.26 1.27 1.28

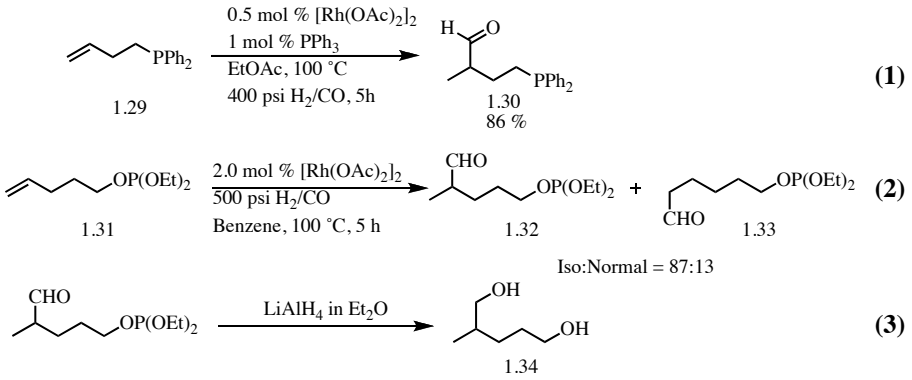
(77:23) desired/other regio- and stereo- isomers

In 1987 Jackson and Perlmutter demonstrated that the stoichiometric incorporation of phosphine ligands led to a complete reversal in iso/normal selectivity for the hydroformylation of terminal alkenes, yielding 86% of exclusively iso product (Scheme 7, eq. 1).[12] Although the resulting phosphinoaldehydes could be functionalized through Horner-Wittig methodology,[13] it was realized that a wider range of chelating groups would be key to bringing this methodology into the mainstream. Jackson and Perlmutter soon followed their discovery with the stoichiometric incorporation of alkyl

[11] Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1990,** *55,* 2138-2151.
[12] Jackson, W. R.; Perlmutter, P.; Suh, G. *J. Chem. Soc., Chem. Commun.,* **1987,** 724-725.
[13] Buss, A. D.; Warren, S. *Tetrahedron Lett.,***1983,** *24,* 3931-3934.

phosphites onto homoallylic alcohols for the iso-selective hydroformylation of olefins.[14] As demonstrated (Scheme 7, eq. 2), the chelate model was effective even with this longer chain system, producing a high selectivity of 87:13. More importantly, the DG could be easily removed through a lithium aluminum hydride reduction to afford diol products (Scheme 7, eq. 3).

Scheme 7. Early Work in Directed Hydroformylation



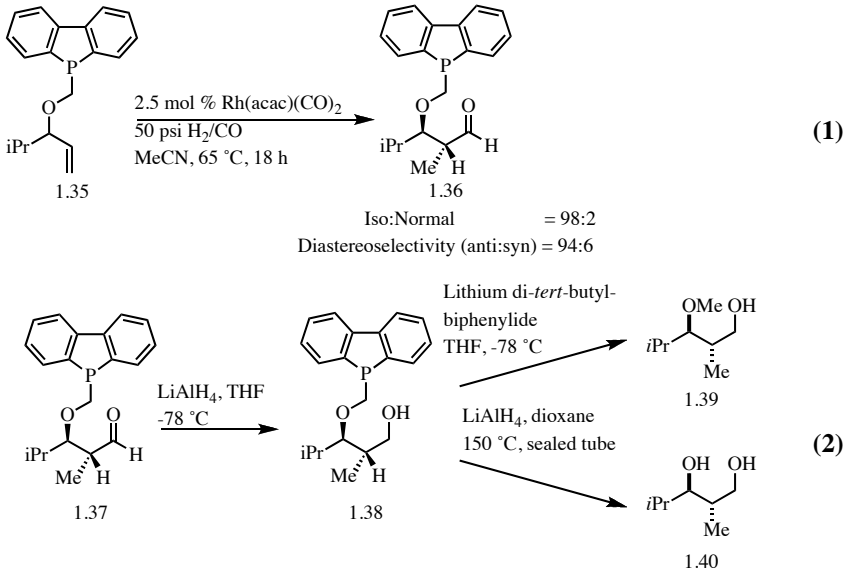
In 1997, Breit described a diastereoselective hydroformylation of substituted allylic alcohols employing an *o*-DPPB (*ortho*-diphenylphosphanylbenzoate) group. This process utilizes a chelation-controlled reaction where the substrate directs the selectivity. More information about these transformations can be found in Chapter 3.

In 2001, Leighton expanded this methodology to encompass the regio- and diastereoselective hydroformylation of allylic ethers.[15] This interesting class of alkenes forms useful propionate aldols, which are poised for further chain extension without additional protection steps. After extensive optimization, the researchers realized the utility of a dibenzophosphol-5-ylmethyl ether as an effective DG. Using this new DG, regioselectivities as high as 98:2 and diastereoselectivities up to 94:6 were observed

[14] Jackson, W. R.; Perlmutter, P.; Tasdelen, E. E. *J. Chem. Soc., Chem. Commun.* **1990,** 763-764.
[15] Krauss, I. J.; Wang, C.-Y.; Leighton, J. L. *J. Am. Chem. Soc.* **2001,** *123,* 11514-11515.

(Scheme 8, eq. 1). This strategy is especially attractive because the DG can be removed to afford either the diol product or a methyl ether protected product (Scheme 8, eq. 2).

Scheme 8. Regio- and Diastereoselective Hydroformylation of Allylic Esters

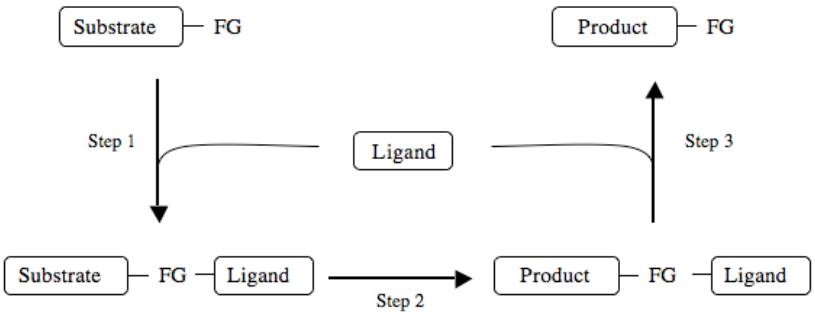


IV. The Discovery of a New Scaffolding Ligand

As seen before, the ideal ligand for a metal catalyst is not always a useful functional group handle for future synthetic transformations. Additional effort must be spent installing and removing traditional DGs, which inherently generate a stoichiometric amount of byproducts.[16] The Tan lab has designed a ligand that binds to a catalyst and substrate reversibly, allowing for a directed reaction to occur using only a catalytic amount of this additive. Employing this catalytic scaffolding ligand approach allows one to utilize common functional groups and still have a selective reaction.

[16] (a) Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27,* 4237-4240. (b) Jackson, W. R.; Perlmutter, P.; Tasdelen, E. E. *Tetrahedron Lett.* **1990**, *31,* 2461-2462. (c) Jackson, W. R.; Perlmutter, P.; Tasdelen, E. E. *J. Chem. Soc., Chem. Commun.* **1990**, *10,* 763-764. (d) Breit, B. *Angew. Chem. Int. Ed.* **1996**, *35,* 2835-2837. (e) Breit, B.; Zahn, S. K. *J. Org. Chem.* **2001**, *66,* 4870-4877. (f) Breit, B.; Demel, P.; Gebert, A. *Chem. Commun.* **2004**, *1,* 114-115.

Scheme 9: Catalytic Directing Group Strategy

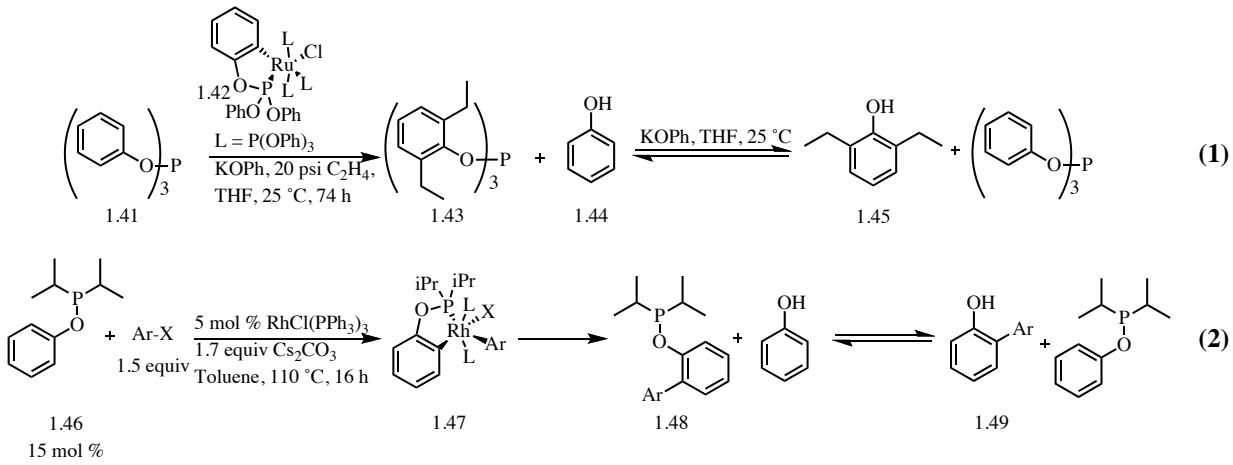


The design of a scaffolding ligand capable of efficient exchange followed by directed reaction has been achieved through careful observation and planning. The two design elements necessary for a potential ligand are: 1) reversible association of substrate and the scaffolding ligand, and 2) effective catalyst-ligand binding (Scheme 9, Step 2). Effective substrate and catalyst binding will lead to an intramolecular pathway; this should yield a more selective and reactive system when compared with the corresponding intermolecular reaction. Once the intramolecular reaction has occurred, the desired product will be attached to the ligand and can be removed through exchange with another substrate molecule to re-enter the catalytic cycle (Scheme 9, Step 3).

Attention was focused on the challenging problem of engineering an equilibrium reaction between the ligand and substrate that would occur below 55 ˚C (a typical reaction temperature for hydroformylation). This temperature range would be ideal because it allows for exchange of the ligand to be competitive with background hydroformylation. Ligand-bound substrate would immediately be available for reaction with the catalyst. Whereas if the exchange occurs only at higher temperatures or occurs very slowly at 55 ˚C, there might be an induction period during which the background

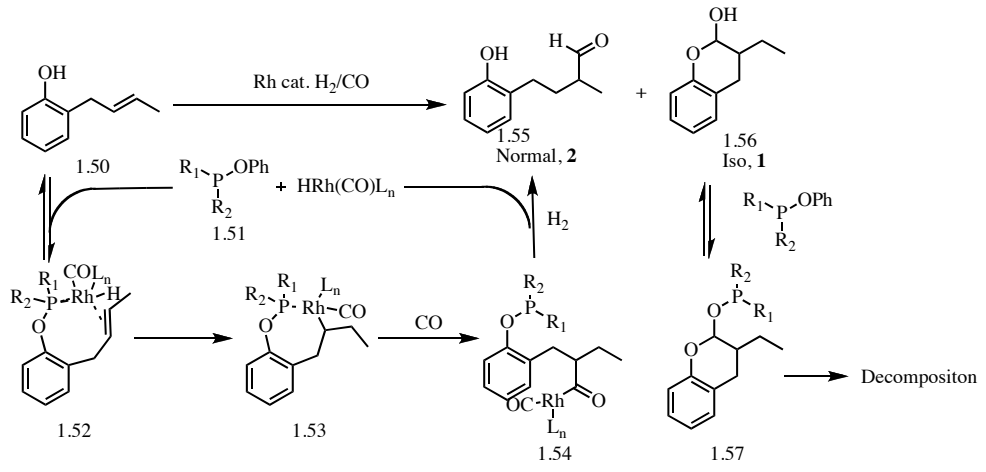
reaction is allowed to proceed before ligand and substrate bind. Background reaction would also become competitive with the turnover of such a ligand.

Scheme 10: Exchange of Phenols at a Phosphorous Center



Literature precedent was seen for the use of phosphinite ligands in catalytic C-H activation. In work done by Lewis,[17] exchange of these phosphinite ligands was observed in the presence of base (Scheme 10, eq. 1). In contrast, exchange occurred *in situ* in the Bedford[18] case to yield a catalytic C-H arylation reaction (Scheme 10, eq. 2).

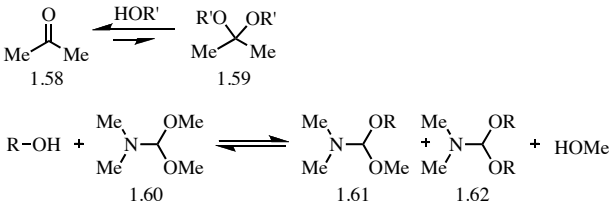
Scheme 11: Catalytic Use of Phosphinites as Directing Groups for Hydroformylation



[17] Lewis, L.N. *Inorg. Chem.* **1985**, *24*, 4433-4435.
[18] Bedford, R.B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669-8682.

Preliminary endeavors in this area focused on the catalytic use of mixed aryl-alkyl phosphinite ligands for the directed hydroformylation of allylic phenol substrates (Scheme 11). Over the course of these studies it was determined that there was a problem of product inhibition. The hydroformylation products would slowly exchange onto the ligand and decompose both parties. This process led to low overall yields (30-60%). A more effective ligand was needed to carry out the desired transformation.

Scheme 12: Exchange of DMF-$(OMe)_2$



Alcohol	**1.60** : **1.61** : **1.62**[a]	$t_{1/2}$
Allyl Alcohol	1.0 : 1.4 : 1.1	< 1 h

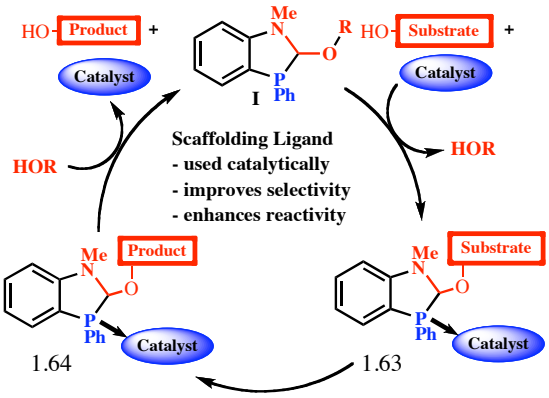
[a]Ratio represents equilibrium using 4 equiv of alcohol

Alcohols are known to reversibly form acetals upon reaction with ketones and aldehydes (Scheme 12). Unfortunately, acetal formation is enthalpically disfavorable and requires acid catalysis at high temperatures, making it undesirable for this strategy.[19] Nevertheless, inspired by this reaction, a related reversible reaction was identified: the exchange of alcohols with *N,N'*- dimethylformamide dimethyl acetal (DMF-$(OMe)_2$). Alcohol exchange with DMF-$(OMe)_2$ is a facile and close to a thermoneutral process (Scheme 12).[20] The rapid rate of exchange is presumably due to the donation of the N_{lp} into the σ^* of the C-O bond. However, it has been demonstrated that nitrogen-based

[19] Vollhardt, K. P. C.; Schore, N. E. *Organic Chemistry: Structure and Function 5th Ed.* W. H. Freeman and company: New York, **2007,** Chapter 17, 778-784.
[20] This reaction was examined by Thomas Lightburn.

ligands are not nearly as efficient in hydroformylation as those containing a phosphorous moiety. Thus, it was decided that in addition to a nitrogen/acetal functional group, a phosphorous atom would be added as a metal binding element. This led to the discovery of scaffolding ligand **I**.

Scheme 13: Discovery of a Scaffolding Ligand

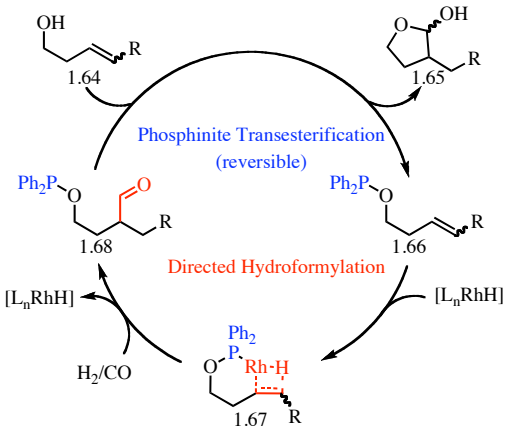


This bifunctional scaffolding ligand contains two independent binding sites: a substrate binding site (shown in red, Scheme 13) and a metal binding domain (shown in blue, Scheme 13). This ligand leads to the intimate association of the metal and substrate, allowing for enhanced control of the selectivity of the transformation. A unique substrate binding site provides the possibility of bonding to a variety of organic functionalities without substantially interfering with the metal binding domain. This ligand is used in reaction sequences described in Chapter 2.

V. Catalytic Directed Hydroformylation

Breit disclosed an approach towards the iso selective hydroformylation of homoallylic alcohols[21] that is similar to the scaffolding ligand strategy described in Chapter 2.[22] The catalytic process analogously relies on covalent, but reversible, substrate binding of the ligand before directed hydroformylation occurs (Scheme 14). In the course of their studies, Breit and coworkers found that a simple phosphinite ligand could be employed in the presence of molecular sieves to effect a reversible exchange with the homoallylic alcohol substrates. These reactions could be carried out under relatively mild conditions, proceeding at near room temperature (40 ˚C) and medium pressure (300 psi).

Scheme 14. Breit's Proposed Reaction Mechanism



The regioselectivity of hydroformylation for this new class of "catalytic directing groups" was comparable to that of stoichiometric reactions (Section III). In some cases this strategy effected regioselectivities as high as 99:1 in favor of the iso regioisomer. The hydroformylation of a terminal olefin (Scheme 15) demonstrates the utility of this strategy. In this case, the reaction bias is completely overturned from the original 27:73 iso/normal to an astounding 99:1 iso selectivity. Although the results disclosed in this

[21] Grünanger, C. U.; Breit, B. *Angew. Chem. Int. Ed.* **2008,** *47,* 7346-7349.
[22] Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008,** *130,* 9210-9211.

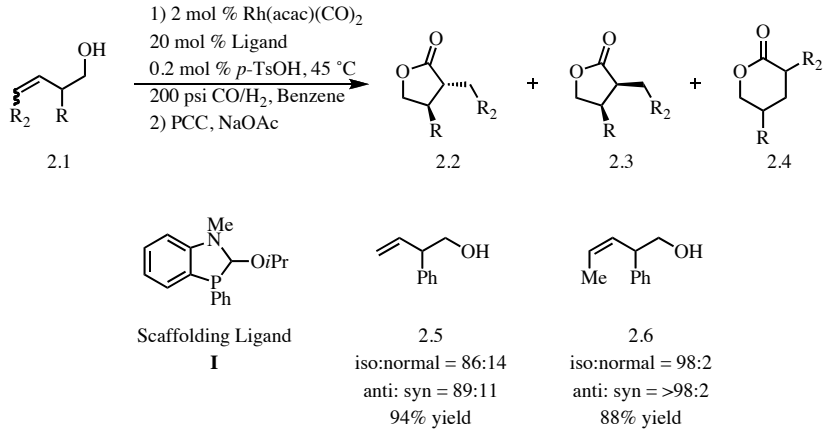
paper are promising, it remains to be seen whether this strategy is broadly applicable to a range of substrates. The covalent bond formed between the phosphorous atom of the ligand and the substrate may lead to a change in electronics of the metal-bound system as the linker moiety is modified, therefore limiting the substrate scope of these reactions.

Chapter 2: Catalytic Scaffolding Ligands in the Hydroformylation of Allylic Sulfonamides

I. Project Perspective

It has been demonstrated in our laboratories that catalytic amounts of scaffolding ligand **I** can be utilized for the directed hydroformylation of olefins to afford high regio- and diastereoselectivities (up to 98:2, Scheme 1).[1] For example, terminal olefin **2.5** is hydroformylated using this strategy in 86:14 regioselectivity, 89:11 diastereoselectivity, and 94% yield. Hydroformylation of the more challenging disubstituted olefin **2.6** provides 98:2 regioselectivity, >98:2 diastereoselectivity, and 88% yield.

Scheme 1. Scaffolding Ligand Directed Hydroformylation of Homoallylic Alcohols



Our goal in this project was to expand the substrate scope of this strategy to encompass a variety of common and useful functional groups. Scaffolding ligand **I** was utilized in the synthesis of β-amino-aldehydes (Mannich Products[2]) through the highly

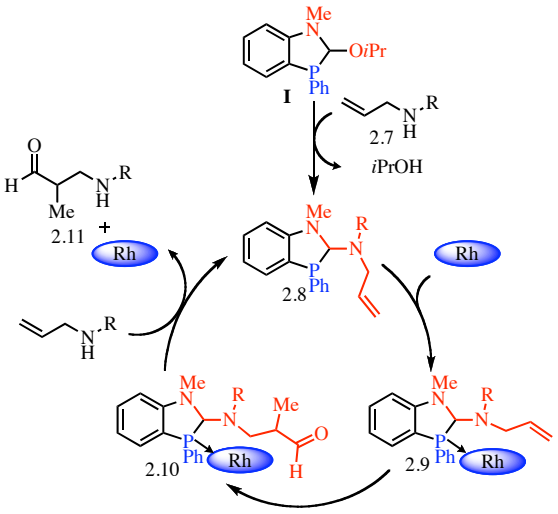
[1] Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008,** *47,* 7346-7347.
[2] (a) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797-5815. (b) Cordova, A. *Acc. Chem. Res.* **2004**, *37,* 102-112. (c) Gnas, Y.; Glorius, F. *Synthesis.* **2006**, 1899-1930.

regioselective hydroformylation of protected amines. This work was done in collaboration with Amanda Worthy.

II. Hypothesized Catalytic Cycle

We envisioned the directed hydroformylation occurring through the catalytic cycle below (Scheme 2).

Scheme 2. Proposed Catalytic Cycle for Allylic Sulfonamide Hydroformylation

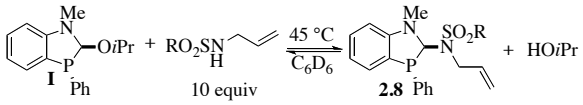


Initial exchange of a substrate onto **I** generates the substrate bound ligand **2.8**. Ligand **2.8** can serve as a bidentate ligand to rhodium, binding through the phosphorous center and olefin. The resulting directed hydroformylation proceeds with enhanced selectivity and reactivity. Once the desired reaction has occurred, it is necessary for ligand-bound product to exchange readily with starting material to form **2.8** and re-enter the catalytic cycle.

III. Exchange Studies to Determine the Viability of New Substrates

Preliminary studies done by Amanda Worthy and Kian Tan indicated that carbamates and amides did not exchange with **I**, therefore failing the first test of viability. Meanwhile, sulfonamides were readily incorporated onto the ligand (Table 1). We believe the success of the sulfonamide is related to the similarity in pK_a to alcohols. It was found that as the pK_a of the substrate decreased, the rate of exchange increased (Table 1).

Table 1. Relative Rates of Exchange with Sulfonamides



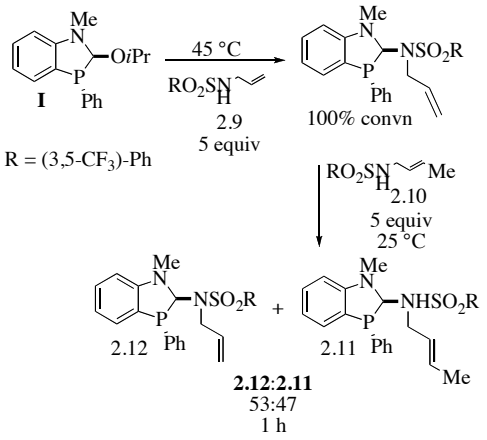
R	Conversion at 6 h
p-OMe-Ph	0
p-Me-Ph	0
p-NO_2-Ph	23%[a]
(3,5-CF_3)-Ph	69%[b]

[a] >95% conversion reached in 6 days
[b] >95% conversion reached in 13 h

Although the initial exchange with ligand **I** is important, efficient catalysis cannot be achieved without also establishing that exchange of sulfonamide bound ligand **2.8** and free sulfonamide substrate occurs. To test this aspect, substrate **2.9** was mixed with ligand **I** to preform **2.12**. A subsequent step in which substrate **2.10** was added to **2.12**

demonstrated that the exchange to form ligand **2.11** was rapid, with a 53:47 mixture of **2.12** and **2.11** forming in 1 h at 25 ˚C (Scheme 3).[3]

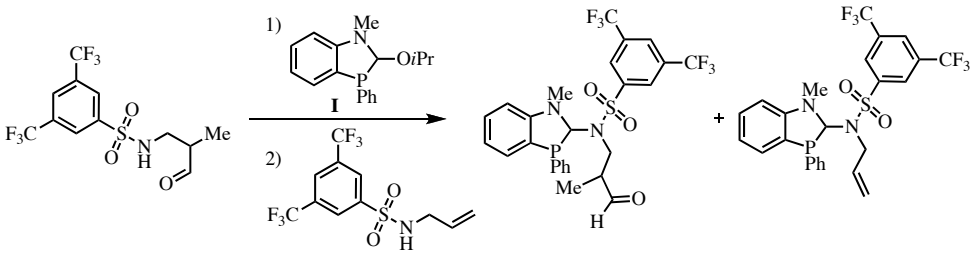
Scheme 3: Substrate Exchange



Displacement of product from the ligand is also an important step in the catalytic cycle. Once the aldehyde is formed, a new substrate molecule must take its place to allow the ligand to re-enter the catalytic cycle. To verify that this happens, product isolated from hydroformylation of **2.9** was mixed with ligand **I** at 45 ˚C in C_6D_6. Exchange occurs rapidly to yield a mixture of **I** and **2.14,** as well as an unidentified decomposition product (Table 2). Ligand **2.11** was formed almost immediately upon addition of substrate **2.9**, suggesting that substrate **2.9** has a higher affinity for **I** than the product, likely due to the increased sterics of the product.

[3] At equilibrium the ratio of **2.12** to **2.11** is 43:57.

Table 2. Product/Substrate Exchange

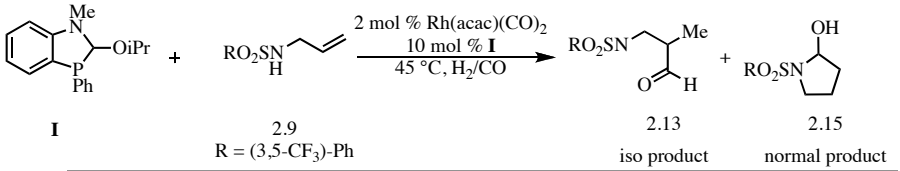


Time	Temp (˚ C)	% **I**[a]	% **2.14**[a]	% **2.11**[a]	% Decomposition[a]
1 h	45	31	45	0	24
2 h	45	31	45	0	24
Added Starting Material (III)					
5 min	25	42	Trace	36	23
20 min	25	32	0	40	28
4.5 h	25	24	0	48	29

[a]Determined by ^{31}P NMR

IV. Optimization of Sulfonamide Hydroformylation

Table 3. Optimization of Sulfonamide Hydroformylation



I 2.9 R = (3,5-CF_3)-Ph 2.13 iso product 2.15 normal product

entry	pressure (psi)	regioselectivity (**VI:VII**)	conversion (%)[b]
1[a]	200	50:50	>95
2	200	60:40	>95
3[c]	200	90:10	86
4[c]	100	88:12	83
5[c]	300	95:5	>95
6[c]	400	97:3	>95

[a]Reaction run with 4% PPh_3 as the ligand. [b]Conversion determined by ^{1}H NMR. [c]**2.9** and **I** were exchanged at 55 °C prior to hydroformylation.

Having demonstrated that ligand exchange occurs, we investigated the regioselective hydroformylation of **2.9** (Table 3). Hydroformylation employing triphenylphosphine as the ligand leads to complete conversion and a 50:50 mixture of normal and iso products (Table 3, entry 1). This control reaction demonstrates the substrate's inherent selectivity because triphenylphosphine can not bind to the substrate. Similar terminal substrates have been shown to favor normal products, suggesting that in this case there is a moderate directing group effect from the sulfonamide functionality.[4] Hydroformylation in the presence of scaffolding ligand **I** yields a slightly increased iso:normal selectivity (Table 3, entry 2). Rate acceleration was observed in the exchange

[4] For examples of amide directed hydroformylation see: (a) Ojima, I.; Zhang, Z. *J. Org. Chem.* **1988**, *53,* 4422-4425. (b) Ojima, I.; Zhang, Z. *J. Organomet. Chem.* **1991**, *417,* 253-276. (c) Campi, E. M.; Chong, J. M.; Jackson, W. R.; Van Der Schoot, M. *Tetrahedron* **1994**, *50,* 2533-2542. (d) Dickson, R. S.; Bowen, J.; Campi, E. M.; Jackson, W. R.; Jonasson, C. A. M.; McGrath, F. J.; Paslow, D. J.; Polas, A.; Renton, P.; Gladiali, S. *J. Mol. Cat. A.* **1999**, *150,* 133-146.

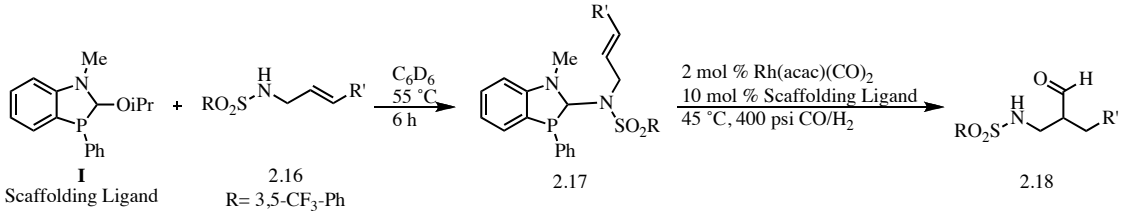
of substrate **2.10** onto ligand **2.12** (Scheme 3) when compared to the original exchange of substrate **2.9** onto the ether substituted ligand **I**. Based on this result, a preexchange experiment was carried out in which the ligand was completely converted to the substrate-bound form **2.12**. This mixture of **2.12** and excess substrate **2.9** was hydroformylated under standard conditions to yield a significantly higher iso:normal selectivity of 90:10 (Table 3, entry 3). Further optimization of the H_2/CO pressure to 400 psi further enhances the selectivity (Table 3, entry 6). We hypothesize that the increased CO pressure inhibits the background hydroformylation reaction through inhibition of olefin binding.[5] This inhibition of background hydroformylation allows the directed reaction to compete more effectively. Increased CO pressure may also facilitate ligand exchange on the metal, which is important in the turnover of the substrate.

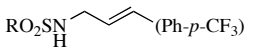
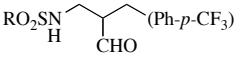
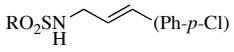
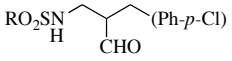
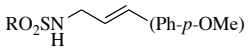
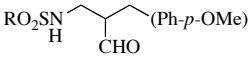
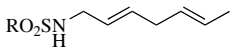
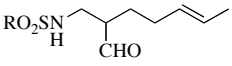
V. Evaluation of Substrate Scope

With optimized reaction conditions in hand, it was necessary to evaluate the reaction tolerance with regard to functional groups. In particular, focus was placed on expanding the scope to include disubstituted olefins.

[5] a) van Leeuwen, P.W.N. M; Casey, C.P.; Whiteker, G.T. *Rhodium Catalyzed Hydroformylation*; Leeuwen, P.W.N.M, Claver, C., Eds.; Kluwer Academic Publishers: Norwell, MA, 2001; Chapter 4, pp 63-106. b) van Rooy, A.; Orij, E. N.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics*, **1995**, *14*, 34-43.

Table 4: Evaluation of Sulfonamide Substrate Scope



entry	substrate	product	regioselectivity[a]	yield (%)[e]
1	 2.19	 2.20	98:2 (12:88)[b]	92
2	 2.21	 2.22	99:1 (13:87)[b]	69
3	 2.23	 2.24	97:3[c] (22:78)[b,c]	87
4	 2.25	 2.26	>95:5[d]	75

Conditions: [a] 1) Substrate, 10 mol % **I,** 55 °C, benzene, 6 h.; 2) 2 mol % $Rh(acac)(CO)_2$, 400 psi CO/H_2, 45 °C, 5% THF/benzene; Regioselectivity of aldehyde:hemiaminal determined by SFC analysis. [b]Regioselectivity for reactions run with 2 equiv PPh_3 with respect to Rhodium instead of **I.** [c]Hydroformylation performed in 10% THF/benzene with 3 mol % $Rh(acac)(CO)_2$ at 55 °C. [d]Benzene as solvent; selectivity determined by analysis of crude ^1H NMR. [e]Isolated yields of the mixture of regioisomers.

In general, styrenes have a strong preference to form the aldehyde at the α-position with respect to the aryl group.[6] This selectivity was completely overturned using scaffolding ligand **I** and led almost exclusively to the β-aldehydes in a variety of styrene derived substrates **2.19**, **2.21**, and **2.23** (Table 4, entry 1-3). For example, in entry 1 (Table 4), scaffolding ligand **I** provides 98:2 iso/normal selectivity, while

[6] van der Veen, L. A.; Boele, M. D. K.; Bregman, F. R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J.; Schenk, H.; Bo, C. *J. Am. Chem. Soc.* **1998,** *120,* 11616-11626. and references cited therein

triphenylphosphine yields a ratio of 12:88. The electronic perturbations in these styrenyl substrates did not strongly affect the regioselectivity of this reaction; leading to the conclusion that the directing group effect outweighs the electronic effects of the substrate.

The chemoselectivity of the reaction was examined by hydroformylation of skip diene substrate **2.25**. Notably, employing triphenylphosphine as a ligand led to an intractable mixture; while use of scaffolding ligand **I** yields a single product cleanly (Table 4, entry 4).

VI. Conclusions

The use of scaffolding ligand **I** leads to the highly regioselective hydroformylation of allylic sulfonamides to form β-amino-aldehydes. In some cases inherent selectivity can be completely reversed through this strategy. This directing group strategy also has the advantage of high chemoselectivity as demonstrated by the clean reaction of only the allylic olefin in a skip-diene substrate.

VII. Experimental

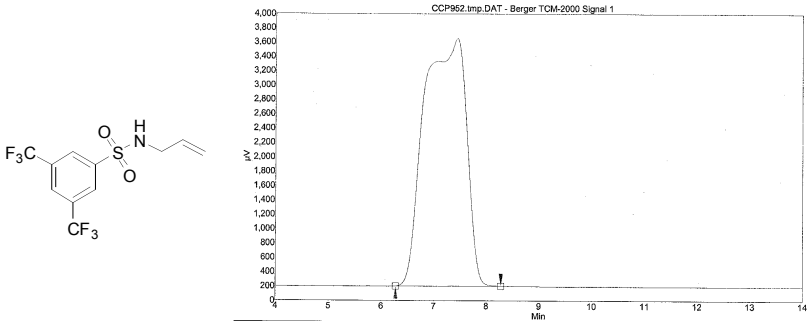
General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Lithium reagents were titrated against 2-pentanol or 2,6-di-*tert*-butyl-4-methylphenol (BHT) using 1,10-phenanthroline as the indicator. Flash column chromatography was performed using EMD Silica Gel 60 (230-400 mesh) and ACS grade solvents as received from Fisher Scientific. All experiments were performed

in oven or flame dried glassware under an atmosphere of nitrogen or argon using standard syringe and cannula techniques, except where otherwise noted. All reactions were run with dry, degassed solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). ^{1}H, ^{13}C and ^{31}P NMR were performed on either a Varian Gemini-2000 400 MHz or a Varian Unity 300 MHz instrument. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. C_6D_6 was degassed by three successive freeze-pump-thaw cycles and stored over 3Å molecular sieves in a dry box under a nitrogen atmosphere. All NMR chemical shifts are reported in ppm relative to residual solvent for ^{1}H and ^{13}C and external standard (neat H_3PO_4) for ^{31}P NMR. Coupling constants are reported in Hz. All IR spectra were gathered on a Bruker Alpha FT-IR equipped with a single crystal diamond ATR module and values are reported in cm^{-1}. Analytical supercritical fluid chromatography (SFC) was performed on a Berger Instruments Supercritical Chromatograph equipped with an Alcott auto sampler and a Knauer UV detector using methanol as the modifier. An achiral Princeton SFC 4.6x150 mm silica column (henceforth Silica) with 60Å mesh silica, 6μ particle size was used for analysis of some compounds. All SFC retention times are reported as t_r. HRMS and X-ray crystal structure data were generated in Boston College facilities. Hydroformylation was performed in an Argonaut Technologies Endeavor® Catalyst Screening System using 1:1 H_2/CO supplied by Airgas, Inc.

Substrate Syntheses and Characterization

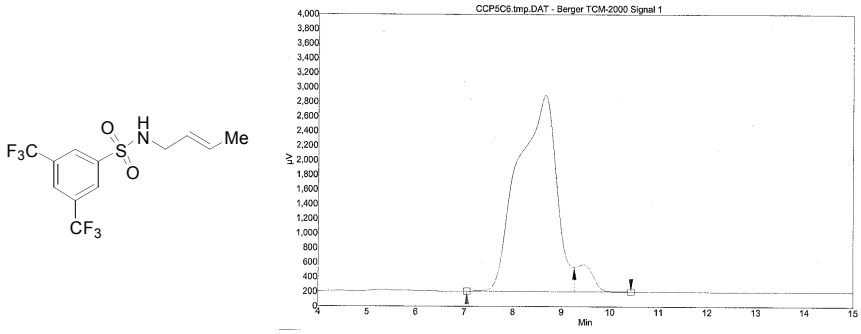
The following compounds were made according to literature procedures and matched reported spectra: *(E)*-but-2-en-1-amine,[7,8,9] 2-Isopropoxy-2,3-dihydro-1*H*-benzo[*d*][1,3]azaphosphole **(1),**[10] *(E)*-but-2-en-1-ol,[11] *(E)*-1-bromobut-2-ene,[12] *(E)*-hept-5-en-2-yn-1-ol[13] and (2*E*,5*E*)-hepta-2,5-dien-1-ol.[14]



Cmpd. 2.9: N-allyl-3,5-Bis(trifluoromethyl)benzenesulfonamide.[15] To a flame-dried round bottom flask was added 3,5-bis-trifluoromethylphenylsulphonyl chloride (4.00 g, 12.8 mmol) and CH_2Cl_2 (50 mL). The solution was cooled to 0 ˚C and allyl amine (4.78 mL, 63.9 mmol) was added dropwise. The solution was allowed to warm to room temperature. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with 1:1 brine/H_2O (2x30 mL) and brine (1x30 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. Chromatography (15% EtOAc/Hex) afforded a white solid (4.15 g, 97%). **SFC** (AS-H, 1.0 mL/min, 1.0% MeOH, 220 nm, 150 bar, 50

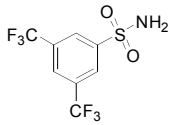
[7] Calsen, P. H. J.; Jorgensen, K.B. *J. Heterocyclic Chem.* **1997**, *34*, 797-806.
[8] Nishikawa, Y.; Nakamura, Y.; Kawaguchi, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 155-160.
[9] Hamada, J., Tsunashima, S., Sato, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 662-666.
[10] Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210-9211.
[11] Haynes, R. K.; Au-Yeung, T.; Chan, W.; Lam, W.; Li, Z.; Yeung, L.; Chan, A. S. C.; Li, P.; Koen, M.; Mitchell, C. R.; Vonwiller, S.C. *Eur. J. Org. Chem.* **2000**, *18*, 3205-3216.
[12] Loughin, W. A.; Haynes, R. K. *Aust. J. Chem.* **1995**, *48*, 651-661.
[13] Davies, S. G.; Haggitt, J. R.; Ichihara, O.; Kelly, R. J.; Leech, M. A.; Price, M. A. J.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2004**, *2*, 2630-2649.
[14] Pickard, S. T.; Smith, H. E.; Polavarapu, P. L.; Black, T. M.; Rauk, A.; Yang, D. *J. Am. Chem. Soc.* **1992**, *114*, 6850-6857.
[15] Brummond, K.M.; Chen, H.; Mitasev, B.; Casarez, A. D. *Org. Lett.* **2004**, *6*, 2161-2163.

˚C) t_r = 7.44 min; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.32 (s, 2H), 8.08 (s, 1H), 5.71 (m, 1H), 5.16 (m, 2H), 4.91 (t, 1H, *J* = 5.9), 3.72 (ddd, 2H, *J* = 12.0, 6.0, 1.3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.4, 133.1 (q, *J* = 34.5), 132.3, 127.5, 126.4, 122.6 (q, *J* = 273.6), 118.6, 46.0; **IR**: 3274, 3087, 1626, 1430, 1362, 1340, 1281, 1196, 1175, 1160, 1132, 1110, 906, 886, 697, 682, 645, 589, 515 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_9F_6NO_2S$ $[M+H]^+$: 334.0336, found: 334.0340.; **m.p.** 90-91 ˚C.



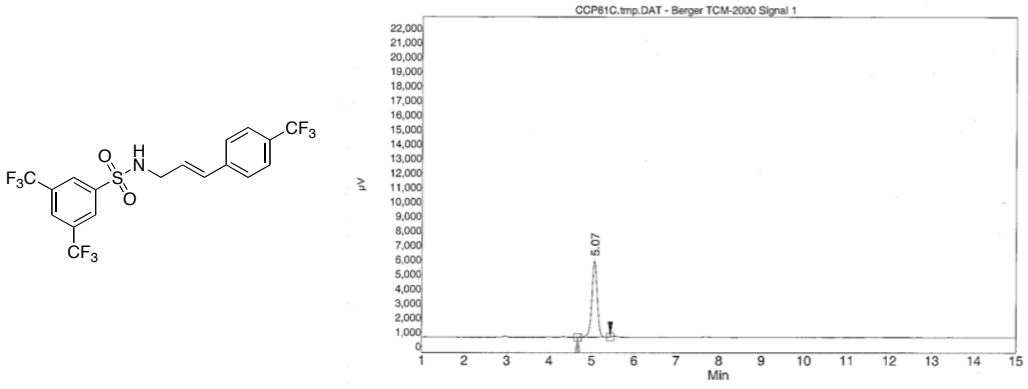
Cmpd. 2.10: cis/trans-(18:82 mixture)-N-(But-2-enyl)-3,5-bis(trifluoromethyl) benzenesulfonamide. To a flame-dried round bottom flask was added but-2-en-1-amine hydrochloride (4.11 g, 37.5 mmol), triethylamine (713 μL, 5.12 mmol) and CH_2Cl_2 (150 mL). The solution was cooled to 0 ˚C and 3,5-bis-trifluoromethylphenylsulphonyl chloride (11.7 g, 37.5 mmol) was added. The reaction was allowed to warm to room temperature. The solution was diluted with EtOAc (50 mL) and washed with 1:1 brine/H_2O (2x50 mL) and brine (1x50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. Chromatography (CH_2Cl_2) afforded a white solid (5.36 g, 41.0%). **SFC** (AS-H, 1.0 mL/min, 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) t_r = 8.67 min; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.30 (s, 2H), 8.07 (s, 1H), 5.62 (m, 1H), 5.30 (m, 1H),

4.62 (s, 1H), 3.75 (app. t, 0.4H, J = 6.4), 3.65 (ddd, 2H, J = 12.5, 6.2, 1.1), 1.61 (d, 3H, J = 5.3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.7, 133.1 (q, J = 33.7), 131.1, 127.6, 126.3, 125.0, 122.6 (q, J = 272.8), 45.7, 17.7; **IR**: 3277, 3058, 1626, 1359, 1342, 1279, 1265, 1161, 1141, 1110, 904, 735, 698, 681, 590, 414 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{11}F_6NO_2S$ $[M+H]^+$: 348.0493, found: 348.0502; **m.p.** 89-94 ˚C.



Cmpd. 2.27: 3,5-Bis(trifluoromethyl)benzenesulfonamide.[16] 3,5-bis-trifluoromethylphenyl sulphonylchloride (1.0 g, 3.2 mmol) was suspended in water in a round bottom flask. Concentrated aqueous ammonium hydroxide (1.3 mL, 32 mmol) was added. The mixture was heated to 100 ˚C. After reaching 100 ˚C, the reaction was cooled to room temperature and concentrated. Excess water was removed by azeotroping the product with toluene three times to yield a white solid (1.0 g, 100%). **^{1}H NMR** ($CDCl_3$, 300 MHz)δ 8.39 (s, 2H), 8.09 (s, 1H), 4.99 (s, 2H); **IR**: 3356, 3262, 1323, 1312, 1277, 1266, 1198, 1163, 1131, 907, 731, 699, 682 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_8H_5F_6NO_2S$ $[M+H]^+$: 294.0023, found: 294.0037.

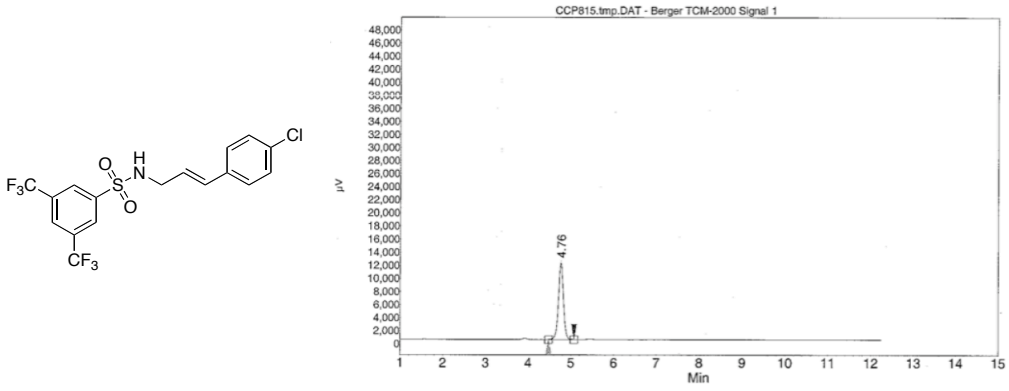
[16] Yuriev, E.; Kong, D. C. M.; Iskander, M. N. *Eur. J. Med. Chem.* **2004**, *39*, 835-847.



Cmpd. 2.19: (*E*)-3,5-Bis(trifluoromethyl)-*N*-(3-(4-(trifluoromethyl)phenyl)allyl) benzenesulfonamide.[17] To a flame dried 2-neck round bottom flask fitted with a reflux condenser was added *N*-allyl-3,5-bis(trifluoromethyl)benzenesulfonamide (1.50 g, 4.50 mmol) followed by palladium(II) acetate (50.5 mg, 0.225 mmol) and tri(*o*-tolyl)phosphine (137 mg, 0.450 mmol). The flask was temporarily placed under vacuum and refilled with nitrogen three times to remove any oxygen followed by addition of acetonitrile (8.4 mL), triethylamine (1.26 mL, 9.01 mmol) and 4-iodobenzotrifluoride (0.66 mL, 4.50 mmol). The reaction mixture was placed in a preheated 90 ˚C oil bath and stirred for 3 h to yield an orange solution. The reaction was cooled below reflux and a second portion of each: palladium(II) acetate (25.3 mg, 0.113 mmol), tri(*o*-tolyl)phosphine (68 mg, 0.225 mmol) and 4-iodobenzotrifluoride (0.28 mL, 1.89 mmol) was added and heated for an additional 16 h. The reaction mixture was diluted with H_2O (28 mL) and extracted with EtOAc (3x20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to yield a yellow oil that was dry loaded (CH_2Cl_2) onto silica gel. Chromatography (15-25% EtOAc/Hex) yielded a light yellow solid (925 mg, 47%). **SFC** (Silica, 5.0 mL/min, 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) t_r = 5.07 min; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.24 (s, 2H), 7.96 (s, 1H), 7.46 (d, 2H, J = 8.4), 7.26 (d,

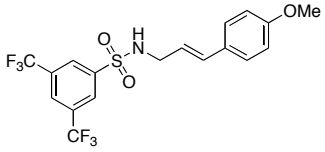
[17] Busacca, C. A.; Dong, Y. *Tet. Lett*. **1996**, *37*, 3947-3950.

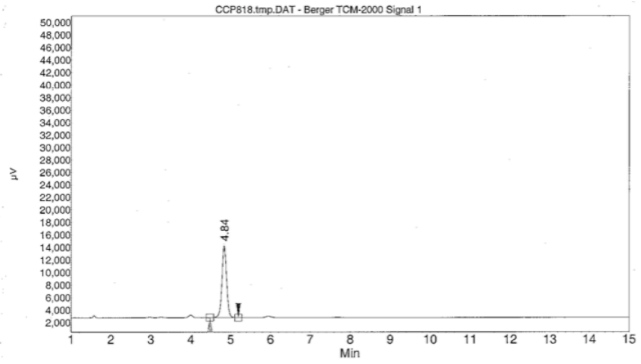
2H, J = 8.4), 6.45 (d, 1H, J = 16.0), 6.05 (dt, 1H, J = 6.0, 16.0), 4.79 (t, 1H, J = 6.0), 3.83 (t, 2H, J = 6.0); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.5, 139.1, 133.3 (q, J = 34.5), 132.7, 130.4 (q, J = 35.2), 127.5, 126.8, 126.5, 126.0, 125.9, 124.2 (q, J = 275.9), 122.5 (q, J = 273.6), 45.6; **IR**: 3290, 3089, 2925, 2854, 1618, 1416, 1360, 1327, 1279, 1160, 1067, 725, 699, 682 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{18}H_{12}F_9NO_2S$ $[M]^{+\bullet}$: 477.0445, found: 477.0447; **m.p.** 136-138 ˚C.



Cmpd. 2.21: (*E*)-*N*-(3-(4-Chlorophenyl)allyl)-3,5-bis(trifluoromethyl) benzenesulfonamide. The procedure for (*E*)-3,5-bis(trifluoromethyl)-*N*-(3-(4-(trifluoromethyl)phenyl)allyl)benzenesulfonamide was followed except that 4-bromochlorobenzene was used instead of 4-iodobenzotrifluoride. Chromatography (7-25% EtOAc/Hex) yielded a white solid (560 mg, 42%). **SFC** (Silica, 5.0 mL/min, 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) t_r = 4.8 min; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.32 (s, 2H), 8.04 (s, 1H), 7.27 (d, 2H, J = 8.4), 7.17 (d, 2H, J = 8.4), 6.45 (d, 15.9, J = 15.9), 6.00 (dt, 1H, J = 6.3, 15.9), 4.76 (t, 1H, 5.7), 3.85-3.90 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.5, 134.2, 134.2, 132.7 (q, J = 34.5), 133.0, 129.0, 127.8, 127.6, 122.6 (q, J = 272.8), 126.4, 123.8, 45.7; **IR**: 3159, 3085, 2960, 2924, 2853, 1625, 1593, 1492, 1427, 1318,

1296, 1159, 1096, 926, 698, 681, 592 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{17}H_{12}ClF_6NO_2S$ $[M+H]^+$: 443.0182, found: 443.0198; **m.p.** 130-133 ˚C.

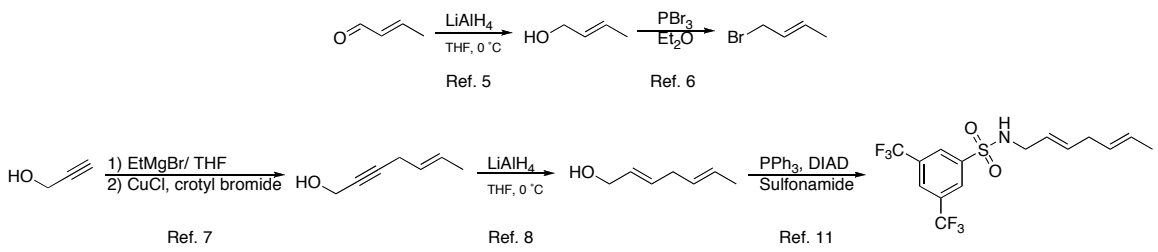


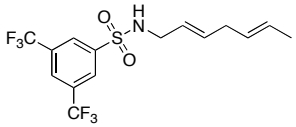


Cmpd. 2.23: (*E*)-*N*-(3-(4-Methoxyphenyl)allyl)-3,5-bis(trifluoromethyl) benzenesulfonamide

The procedure for (*E*)-3,5-bis(trifluoromethyl)-*N*-(3-(4-(trifluoromethyl)phenyl)allyl) benzenesulfonamide was followed except that 4-bromoanisole was used instead of 4-iodobenzotrifluoride. Chromatography (10-25% EtOAc/Hex) yielded an off-white solid (925 mg, 47%). **SFC** (Silica, 5.0 mL/min, 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) t_r = 4.84 min; **^{1}H NMR** (Acetone *d*-6, 400 MHz) δ 8.45 (s, 2H), 8.30 (s, 1H), 7.21 (d, 2H, *J* = 8.8), 6.84 (d, 2H, *J* = 8.8), 6.42 (d, 1H, *J* = 16.0), 5.94 (dt, 1H, *J* =6.4, 16.0), 3.84 (dd, 2H, *J* = 5.6, 6.4). 3.78 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 160.5, 145.4, 133.2, 133.1 (q, *J* = 33.7), 129.8, 128.5, 128.3, 126.9, 123.8 (q, *J* = 272.8), 122.7, 114.8, 55.7, 46.3; **IR**: 3356, 3262, 2958, 2922, 2851, 1626, 1607, 1364, 1323, 1277, 1163, 1132, 1030, 907, 845, 698 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{18}H_{16}F_6NO_3S$ $[M+H]^+$: 440.0753, found: 440.0753; **m.p.** 144-145 ˚C.

Synthesis of *N*-((2*E*,5*E*)-Hepta-2,5-dienyl)-3,5-bis(trifluoromethyl)benzenesulfonamide:





Cmpd. 2.25: *N*-((2*E*,5*E*)-Hepta-2,5-dienyl)-3,5-bis(trifluoromethyl) benzenesulfonamide. 3,5-Bis(trifluoromethyl)benzenesulfonamide (2.93 g, 10.0 mmol), (2*E*,5*E*)-hepta-2,5-dien-1-ol (561 mg, 5.0 mmol) and triphenylphosphine (2.62 g, 10.0 mmol) were dissolved in CH_2Cl_2 (100 mL) in a round bottom flask. DIAD (2.02 g, 10.0 mmol) was added, and the reaction was stirred at room temperature for 2.5 h. The reaction was concentrated. Chromatography (2-7% EtOAc/Hex) afforded light yellow oil that solidified upon standing to yield a white solid (654 mg, 34%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.30 (s, 2H), 8.07 (s, 1H), 5.59 (dt, 1H, *J* = 1.2, 5.1), 5.55-5.63 (m, 3H), 4.56 (t, 1H, *J* = 6.0), 3.67 (dd, 2H, *J* = 1.2, 6.3), 2.59-2,62 (m, 2H), 1.61-1.64 (m, 3H)**; ^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.7, 134.5, 133.1 (q, *J* = 35.4), 127.9, 127.6, 126.9, 126.3, 124.2, 122.6 (q, *J* = 273.5), 45.6, 35.1, 18.0; **IR**: 3289, 3088, 2924, 1625, 1426, 1277, 1134, 1109 969, 904, 843, 698, 680, 631, 589 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{15}H_{16}F_6NO_2S$ $[M+H]^+$: 388.0806, found: 388.0792; **m.p.** 41-43 ˚C.

Exchange Reactions with Sulfonamides

General Exchange Reaction Procedure. The sulfonamide (0.10 mmol) was mixed with ligand **I** (0.01 mmol) in benzene (1.0 mL) and heated to 45 ˚C. The reaction progress was followed by ^{31}P NMR. Ligand **I** ^{31}P NMR: –22.1 ppm.

Table 1, Entry 1: N-Allyl-4-methoxybenzenesulfonamide (22.7 mg, 0.10 mmol) and ligand **I** (2.9 mg, 0.01 mmol) were mixed in benzene (1.0 mL) and heated to 45 ˚C. ^{31}P NMR: –18.7 ppm.

Table 1, Entry 2: N-Allyl-4-methylbenzenesulfonamide (21.1 mg, 0.10 mmol) and ligand **I** (2.9 mg, 0.01 mmol) were mixed in benzene (1.0 mL) and heated to 45 ˚C. ^{31}P NMR: –18.8 ppm.

Table 1, Entry 3: N-Allyl-4-nitrobenzenesulfonamide (24.2 mg, 0.10 mmol) and ligand **I** (2.9 mg, 0.01 mmol) were mixed in benzene (1.0 mL) and heated to 45 ˚C. ^{31}P NMR: –17.9 ppm.

Table 1, Entry 4: N-Allyl-3,5-bis(trifluoromethyl)benzenesulfonamide (33.3 mg, 0.10 mmol) and ligand **I** (2.9 mg, 0.01 mmol) were mixed in benzene (1.0 mL) and heated to 45 ˚C. ^{31}P NMR: –17.8 ppm.

Exchange Reactions with Product/Substrate

General Exchange Reaction Procedure. The product, N-(2-methyl-3-oxopropyl)-3,5-bis(trifluoromethyl)benzenesulfonamide (0.05 mmol) was mixed with ligand **I** (0.01 mmol) in benzene *d*-6 (1.0 mL) and heated to 45 ˚C for 2 h. The reaction progress was followed by ^{31}P NMR. N-allyl-3,5-bis(trifluoromethyl)benzenesulfonamide (0.05 mmol) was added and reaction progress was followed by ^{31}P NMR at 25 ˚C.

Optimization of Iso Selective Hydroformylation

General Optimization Procedure. The Endeavor was charged with 500 uL of benzene per reaction well to fill the void volume between reactor wall and reaction tube, and oven dried glass reaction vials were placed in the Endeavor. The Endeavor was sealed and purged with nitrogen (4x100 psi). The necessary injection(s) were made (see below). The Endeavor was purged with nitrogen (1x100 psi), stirring was started at 250 rpm, and the Endeavor was heated to 45 ˚C and held for 10 minutes. Stirring was stopped, the Endeavor was charged with H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at constant temperature of 45 ˚C and pressure of H_2/CO for 16 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction vials were removed from the Endeavor, a solution of trimethoxybenzene (100 μL, 0.2 M) was added, and the sample was concentrated. ^{1}H NMRs were taken to determine conversion and selectivities. The reaction was chromatographed to determine isolated yield. SFC analysis of the products was used to determine regioselectivities.

Table 3, Entry 1: The General Optimization Procedure was followed. A solution of N-allyl-3,5-bis(trifluoromethyl)benzenesulfonamide (66.7 mg, 0.20 mmol), triphenylphosphine (4.0 mol %, 2.1 mg, 0.008 mmol) and dicarbonylacetylacetonato rhodium(I) (2.0 mol %, 1.0 mg, 0.004 mmol) in benzene (1.50 mL) was prepared in a dry box and injected into the Endeavor via syringe. An additional 500 μL of benzene was added to wash the injection port. The Endeavor was kept at a constant H_2/CO pressure of 200 psi.

Table 3, Entry 2: The General Optimization Procedure was followed. A solution of N-allyl-3,5-bis(trifluoromethyl)benzenesulfonamide (66.7 mg, 0.20 mmol), ligand **1** (10

mol %, 5.7 mg, 0.02 mmol) and dicarbonylacetylacetonato rhodium(I) (2.0 mol %, 1.0 mg, 0.004 mmol) in benzene (1.50 mL) was prepared in a dry box and injected into the Endeavor via syringe. An additional 500 μL of benzene was added to wash the injection port. The Endeavor was kept at a constant H_2/CO pressure of 200 psi.

Table 3, Entry 3: The General Optimization Procedure was followed. N-allyl-3,5-bis(trifluoromethyl)benzenesulfonamide (66.7 mg, 0.20 mmol) and ligand **1** (10 mol %, 5.7 mg, 0.02 mmol) in benzene *d*-6 (600 μL) was heated to 55 ˚C for 6 h. The solution was concentrated in a dry box. The resulting white solid, dicarbonylacetylacetonato rhodium(I) (2.0 mol %, 1.0 mg, 0.004 mmol) and benzene (1.50 mL) were mixed in a dry box and injected into the Endeavor via syringe. An additional 500 μL of benzene was added to wash the injection port. The Endeavor was kept at a constant H_2/CO pressure of 200 psi.

Table 3, Entry 4: The procedure for Table 2, Entry 3 was followed except the Endeavor was kept at a constant H_2/CO pressure of 100 psi.

Table 3, Entry 5: The procedure for Table 2, Entry 3 was followed except the Endeavor was kept at a constant H_2/CO pressure of 300 psi.

Table 3, Entry 6: The procedure for Table 2, Entry 3 was followed except the Endeavor was kept at a constant H_2/CO pressure of 400 psi.

Hydroformylation Substrate Scope

General Hydroformylation Procedure. The Endeavor was charged with 500 μL of benzene per reaction well to fill the void volume between reactor wall and reaction tube, and oven dried glass reaction vials were placed in the Endeavor. The Endeavor was

sealed and purged with nitrogen (4x100 psi). The necessary injection(s) were made (see below). The Endeavor was purged with nitrogen (1x100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at reaction temperature for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at constant reaction temperature and pressure of 400 psi H_2/CO for 16 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction vials were removed from the Endeavor and a solution of trimethoxybenzene (100 μL, 0.2 M) was added and the sample was concentrated. ^{1}H NMRs were taken to determine conversion and selectivities. The reaction was chromatographed to determine isolated yield. SFC analysis of the products was used to determine regioselectivities.

Procedure A. N-Allyl-3,5-bis(trifluoromethyl)benzenesulfonamide (66.7 mg, 0.20 mmol) and ligand 1 (10 mol %, 5.7 mg, 0.02 mmol) in benzene *d*-6 (600 μL) was heated to 45 ˚C for 6 h. The solution was concentrated in a dry box. The resulting white solid, dicarbonylacetylacetonato rhodium(I) (2.0 mol %, 1.0 mg, 0.004 mmol), and benzene (1.50 mL) were mixed in a dry box and injected into the Endeavor via syringe. An additional 500 μL of benzene was added to wash the injection port. The Endeavor was heated to 45 ˚C.

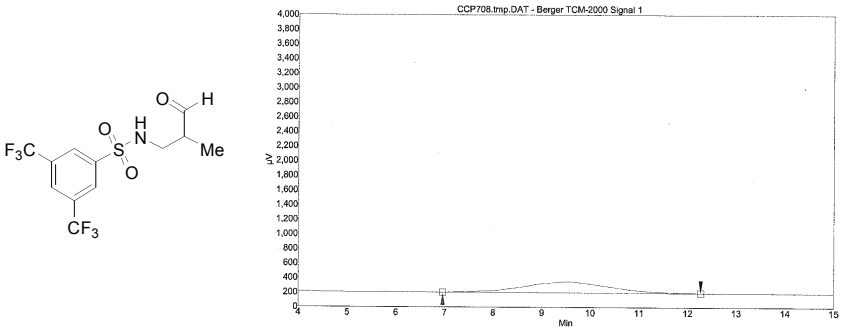
Procedure B. A solution of (*E*)-3,5-bis(trifluoromethyl)-*N*-(3-(4-(trifluoromethyl)phenyl)allyl)benzenesulfonamide (38.2 mg, 0.080 mmol) and ligand **1** (10 mol %, 5.7 mg, 0.02 mmol) in benzene *d*-6 (500 μL) and tetrahydrofuran (100 μL) was heated to 55 ˚C for 16 h. The solution was concentrated in a dry box. The resulting white solid and dicarbonylacetylacetonato rhodium(I) (2.0 mol %, 1.0 mg, 0.004 mmol)

were dissolved in benzene (1.40 mL) and tetrahydrofuran (100 μL) were mixed in a dry box and injected into the Endeavor via syringe. An additional 500 μL of benzene was added to wash the injection port. The Endeavor was heated to 45 ˚C.

Procedure C. A solution of *(E)*-N-(3-(4-methoxyphenyl)allyl)-3,5-bis(trifluoromethyl) benzenesulfonamide (35.2 mg, 0.080 mmol) and ligand **1** (10 mol %, 5.7 mg, 0.02 mmol) in benzene *d*-6 (400 μL) and tetrahydrofuran (200 μL) was heated to 55 ˚C for 16 h. The solution was concentrated in a dry box. The resulting white solid was combined with *(E)*-N-(3-(4-methoxyphenyl)allyl)-3,5-bis(trifluoromethyl)benzenesulfonamide (52.7 mg, 0.12 mmol) and dicarbonylacetylacetonato rhodium(I) (3.0 mol %, 1.3 mg, 0.006 mmol) were dissolved in benzene (1.30 mL) and tetrahydrofuran (200 μL) were mixed in a dry box and injected into the Endeavor via syringe. An additional 500 μL of benzene was added to wash the injection port. The Endeavor was heated to 55 ˚C.

Procedure D. A solution of *N*-((2*E*,5*E*)-hepta-2,5-dienyl)-3,5-bis(trifluoromethyl) benzenesulfonamide (77.4 mg, 0.2 mmol) and ligand **1** (10 mol %, 5.7 mg, 0.02 mmol) in benzene *d*-6 (600 μL) was heated to 45 ˚C for 2 h. The solution was concentrated in a dry box. The resulting white solid, dicarbonylacetylacetonato rhodium(I) (2.0 mol %, 1.0 mg, 0.004 mmol), and benzene (1.50 mL) were mixed in a dry box and injected into the Endeavor via syringe. An additional 500 μL of benzene was added to wash the injection port. The Endeavor was heated to 45 ˚C for 5 h.

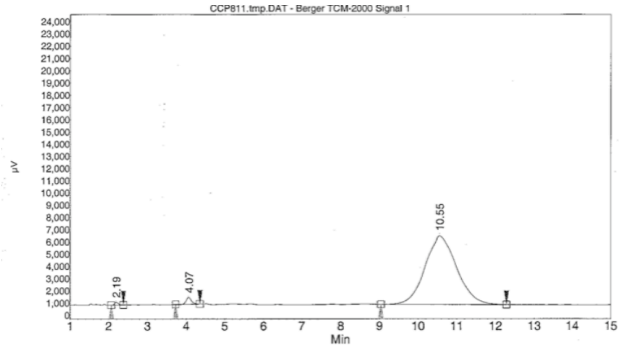
Hydroformylation Results and Product Characterization



Cmpd. 2.13: N-(2-methyl-3-oxopropyl)-3,5-bis(trifluoromethyl)benzenesulfonamide. N-Allyl-3,5-bis(trifluoromethyl)benzenesulfonamide was hydroformylated using General Procedure A. Chromatography (15% EtOAc/Hexanes). **SFC** (AS-H, 1.0 mL/min, 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) t_r = 9.54 min; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.63 (s, 1H), 8.30 (s, 2H), 8.09 (s, 1H), 5.22 (t, 1H, J = 6.1), 3.16 (m, 2H), 2.75 (m, 1H), 1.24 (d, 3H, J = 7.5); **^{13}C NMR** ($CDCl_3$, 100MHz) δ 203.5, 143.1, 133.2 (q, J = 34.3), 127.4, 126.4, 122.6 (q, J = 271.9), 46.7, 43.4, 11.5; **IR**: 3279, 2930, 1721, 1361, 1280, 1163, 1139, 1115, 906, 845, 699, 682, 591 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{12}F_6NO_3S$ $[M+H]^+$: 364.0442, found: 364.0454.

Table 4, Entry 1:

(*E*)-3,5-Bis(trifluoromethyl)-*N*-(3-(4-(trifluoromethyl)phenyl)allyl)benzenesulfonamide was hydroformylated using General Procedure B. Analysis of the crude reaction mixture by ^{1}H NMR showed conversion and selectivity. A mixture of normal and iso products was isolated as a white solid (92.8 mg, 92%) and analyzed by SFC (Silica, 5.0 mL/min 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) to determine the selectivity (98:2).



Index	Name	Time	Width	Height	Area	Area
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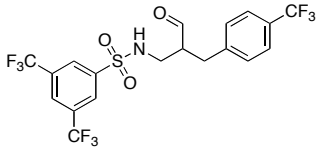
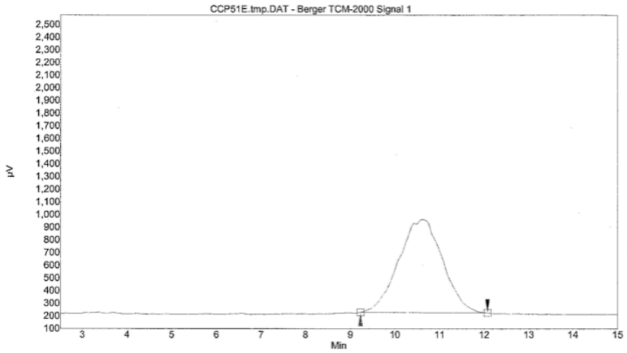
2	FRACTION_	2.19	0.10	231.014	0.466	25.11
1	FRACTION_	4.07	0.14	556.905	1.592	85.82
3	FRACTION_	10.55	0.87	5604.702	97.943	5280.99
Total					100.000	5391.92

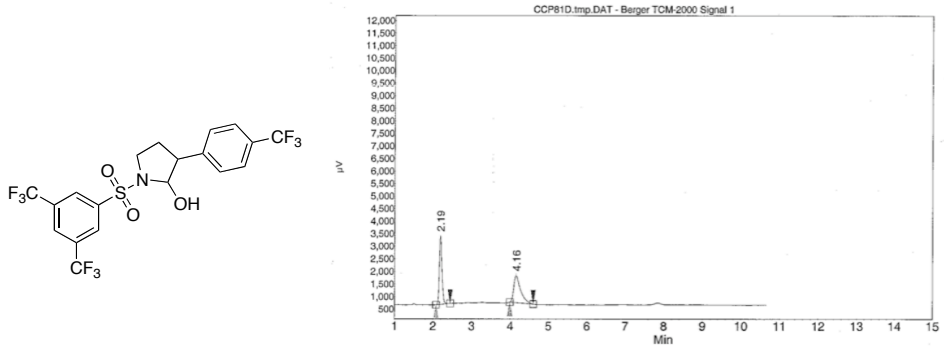




Cmpd. 2.20: *N*-(2-Formyl-3-(4-(trifluoromethyl)phenyl)propyl)-3,5-bis(trifluoromethyl)benzenesulfonamide

SFC (Silica, 5.0 mL/min, 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) t_r = 11.01 min; **^{1}H NMR** (Acetone *d*-6, 400 MHz) δ 9.41 (s, 1H), 8.40 (s, 2H), 8.38 (s, 1H), 7.62 (d, 2H, *J* = 8.0), 7.48 (d, 2H, *J* = 8.4), 7.13 (s, 1H), 3.26-3.37 (m, 2H), 3.21 (dd, 1H, *J* = 6.8, 14.0), 3.03-3.09 (m, 1H), 2.93 (dd, 1H, 7.6, 14.0)**; ^{13}C NMR** (Acetone *d*-6, 100 MHz) δ 203.1, 144.9, 133.8 (q, *J* = 33.7), 131.3, 129.7 (q, *J* = 32.1), 129.1, 127.9, 126.8, 126.7, 126.0 (q, *J* = 270.5), 124.4 (q, *J* = 272.0), 54.3, 42.8, 33.2; **IR**: 3291, 3090, 2927, 2855, 1724, 1620,

1420, 1360, 1327, 1280, 1162, 1068, 1019, 906, 845, 805, 699, 682, 630 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{19}H_{15}F_9NO_3S$ $[M+H]^+$: 508.0629, found: 508.0628.



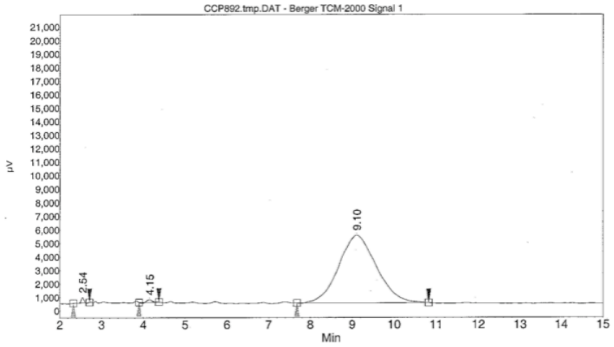
Cmpd. 2.28: 1-(3,5-Bis(trifluoromethyl)phenylsulfonyl)-3-(4-(trifluoromethyl) phenyl)pyrrolidin-2-ol. SFC (Silica, 5.0 mL/min, 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) t_r = 2.2 and 4.2 min (diastereomers); **^{1}H NMR** (Acetone *d*-6, 400 MHz, 46:54 diastereomer ratio) δ 8.55 (s, 1.0H), 8.49 (s, 2.0H), 8.37 (s, 0.6H), 8.34 (s, 1.0H), 7.64 (d, 3.6H, *J* = 8.1), 7.57 (d, 1.4H, *J* = 8.1), 7.51 (d, 2.5H, *J* = 8.1), 5.79-5.84 (m, 1.5H), 5.61 (dd, 1.3H, *J* = 3.1, 5.9), 5.42 (d, 0.4H, *J* = 6.2), 3.72-3.80 (m, 1.4H), 3.50-3.63 (m, 2.7H), 3.43-3.49 (m, 1.3H)**; ^{13}C NMR** (Acetone *d*-6, 100 MHz) δ 145.1, 143.5, 143.4, 142.5, 132.2 (q, *J* = 34.5), 129.9, 128.7 (q, *J* = 20.1), 128.4, 128.1, 128.0, 126.3, 125.5, 124.8, 123.1 (q, *J* = 269.0), 89.9, 84.8, 54.2, 52.9, 49.8, 46.7, 46.1, 27.1; **IR**: 3505, 3089, 2927, 1621, 1360, 1327, 1279, 1163, 1126, 1069, 1046, 907, 844, 700, 682649, 631 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{19}H_{15}F_9NO_3S$ $[M+H]^+$: 508.0629, found: 508.0647.

Table 4, Entry 2:

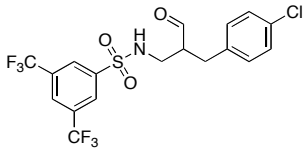
(*E*)-*N*-(3-(4-Chlorophenyl)allyl)-3,5-bis(trifluoromethyl)benzenesulfonamide

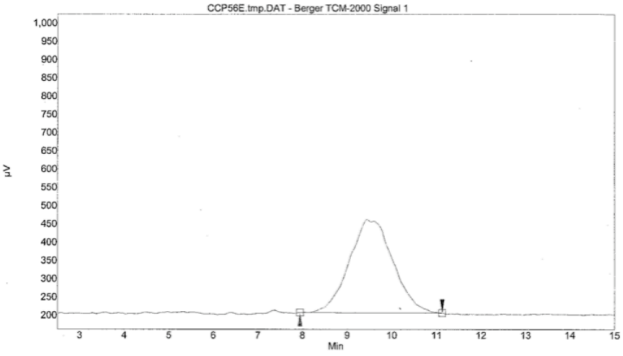
was hydroformylated using General Procedure B. Analysis of the crude reaction mixture by ^{1}H NMR showed conversion and selectivity. A mixture of normal and iso products

was isolated as a white solid (64.9 mg, 69%) and analyzed by SFC (Silica, 5.0 mL/min 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) to determine the selectivity (99:1).



Index	Name	Time [min]	Width [min]	Height [mAU]	Area [%]	Area [mAU*min]
1	FRACTION_	0.05	0.02	4.041	0.002	0.08
2	FRACTION_	0.16	0.02	4.304	0.001	0.06
3	FRACTION_	2.54	0.07	402.117	0.507	26.68
4	FRACTION_	4.15	0.14	190.118	0.409	21.56
5	FRACTION_	9.10	0.96	5023.642	99.081	5219.00
Total					100.000	5267.38

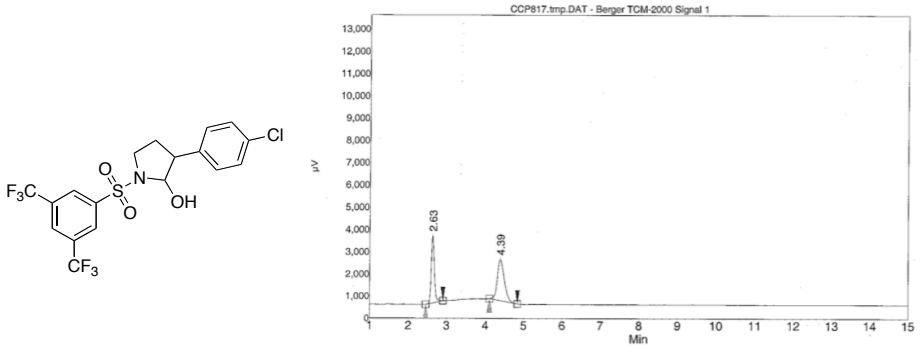




Cmpd. 2.22: *N*-(2-(4-Chlorobenzyl)-3-oxopropyl)-3,5-bis(trifluoromethyl) benzenesulfonamide

SFC (Silica, 5.0 mL/min, 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) t_r = 9.80 min; **^{1}H NMR** (Acetone *d*-6, 400 MHz) δ 9.72 (s, 1H), 8.41 (s, 2H), 8.38 (s, 1H), 7.23- 7.30 (m, 4H), 7.09 (s, 1H), 3.24-3.34 (m, 2H), 3.07-3.12 (m, 1H), 2.95-3.02 (m, 1H), 2.81-2.86 (m, 1H); **^{13}C NMR** (Acetone *d*-6, 100 MHz) δ 203.2, 144.9, 138.7, 133.7 (q, J = 34.5), 133.2, 133.1, 129.2, 130.0, 127.7, 124.3 (q, J = 272.8), 54.4, 42.6, 32.8; **IR**: 3293, 3089, 2929,

1723, 1626, 1493, 1411, 1360, 1318, 1279, 1138, 1112, 906, 844, 722, 699, 630 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{18}H_{15}ClF_6NO_3S$ $[M+H]^+$: 474.0365, found: 474.0381.



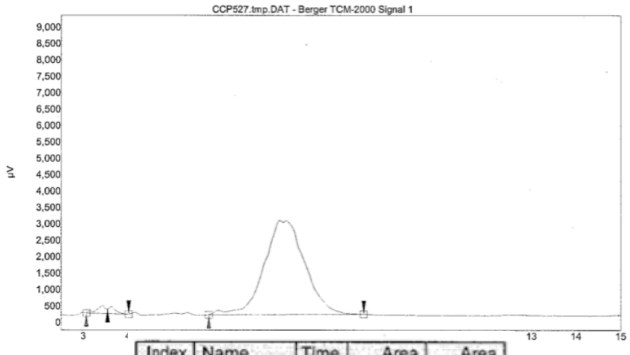
Cmpd. 2.29: 1-(3,5-Bis(trifluoromethyl)phenylsulfonyl)-3-(4-chlorophenyl) pyrrolidin-2-ol

SFC (Silica, 5.0 mL/min, 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) t_r = 2.6 and 4.4 min (diastereomers); **^{1}H NMR** ($CDCl_3$, 300 MHz, 10:1 diastereomer ratio) δ 8.41 (s, 0.2H), 8.28 (s, 1.65H), 8.07 (s, 1.0H), 7.32 (d, 0.25H, *J* = 8.4), 7.19 (d, 2.0H, *J* = 8.6), 7.01 (d, 1.9H, *J* = 8.6), 5.64 (dd, 0.1H, *J* = 3.3, 4.5), 5.47 (dd, 1.0H, *J* = 2.7, 3.3), 3.51-3.63 (m, 2.0H, *J* = 2.4, 6.9), 3.46 (d, 1.1H, *J* = 3.3), 3.33 (dt, 1.2H, *J* = 3.6, 6.9), 2.57 (app. d, 0.1H, *J* = 3.0), 2.41-2.52 (m, 1.0H), 2.21-2.30 (m, 0.2H), 2.03-2.14 (m, 1.0H)**; ^{13}C NMR** ($CDCl_3$, 100 MHz) δ 142.4, 142.2, 137.3, 134.5, 133.8, 133.5, 133.1 (q, *J* = 33.7), 132.9 (q, *J* = 34.5), 130.2, 129.1, 129.0. 128.3, 128.0, 127.5, 126.5, 122.7 (q, *J* = 273.5), 122.6 (q, *J* = 272.8), 90.3, 84.5, 51.3, 49.8, 46.9, 46.4, 29.6, 27.5; **IR**: 3493, 3089, 2960, 1625, 1495, 1360, 1279, 1163, 1138, 1015, 907, 844, 721, 699, 660, 626, 595cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{18}H_{14}ClF_6NO_3SNa$ $[M+Na]^+$: 496.019, found: 496.019.

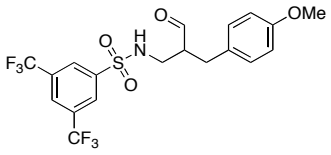
Table 4, Entry 3:

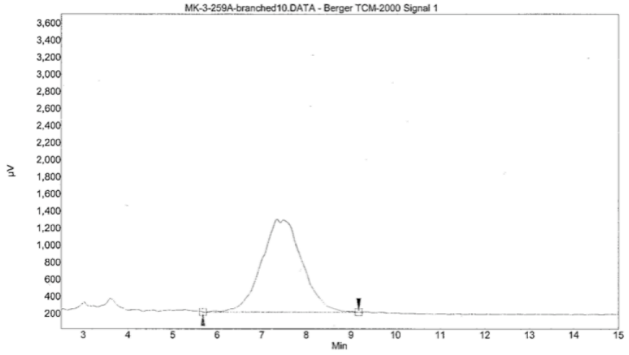
(E)-N-(3-(4-Methoxyphenyl)allyl)-3,5-bis(trifluoromethyl)benzenesulfonamide was hydroformylated using the corresponding General Procedure C. Analysis of the crude

reaction mixture by ^{1}H NMR showed conversion and selectivity. A mixture of normal and iso products was isolated as a white solid (81.4 mg, 87%) and analyzed by SFC (Silica, 5.0 mL/min 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) to determine the selectivity (97:3).



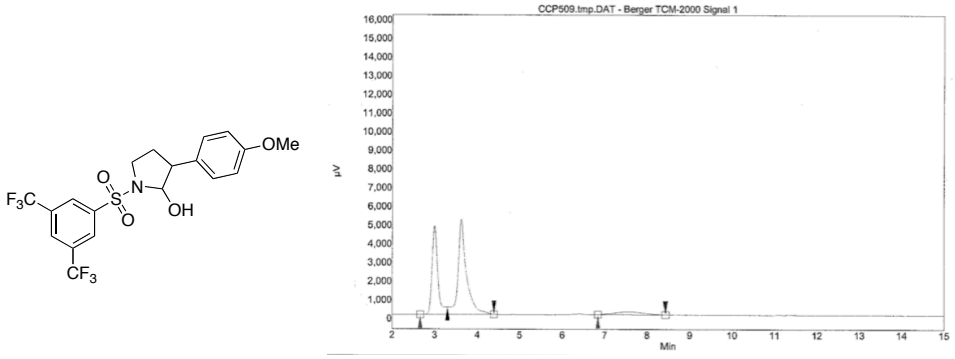
Index	Name	Time	Area	Area
		[Min]	[µV.Min]	[%]
1	UNKNOWN	3.42	55.7	1.783
3	UNKNOWN	3.63	38.9	1.246
2	UNKNOWN	7.38	3027.3	96.971
Total			3121.8	100.000





Cmpd. 2.24: *N*-(2-Formyl-3-(4-methoxyphenyl)propyl)-3,5-bis(trifluoromethyl) benzenesulfonamide. SFC (Silica, 5.0 mL/min, 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) t_r = 8.8 min; **^{1}H NMR** (Acetone *d*-6, 400 MHz) δ 9.69 (s, 1H), 8.25 (s, 2H), 8.07 (s, 1H), 7.08 (d, 2H, *J* =8.4), 6.85 (d, 2H, *J* =8.4), 5.43 (t, 1H, *J* = 6.4), 3.79 (s, 3H), 3.08-3.14 (m, 2H), 3.03 (dd, 1H, *J* = 6.4, 14.4), 2.90-2.97 (m, 1H), 2.74 (dd, 1H, *J* = 8.4, 14.4)**; ^{13}C NMR** (Acetone *d*-6, 100 MHz) δ 203.5, 158.9, 142.9, 133.2 (q, *J* = 34.5), 129.9, 128.6,

127.5, 126.5, 122.6 (q, J = 273.6), 114.6, 55.4, 53.5, 41.5, 32.05; **IR**: 3295, 3086, 2936, 2840, 1721, 1613, 1585, 1513, 1422, 1359, 1277, 1248, 1133, 1034, 905, 843, 808, 699, 681, 630, 589 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{19}H_{18}F_6NO_4S$ $[M+H]^+$: 470.0861, found: 470.0844.

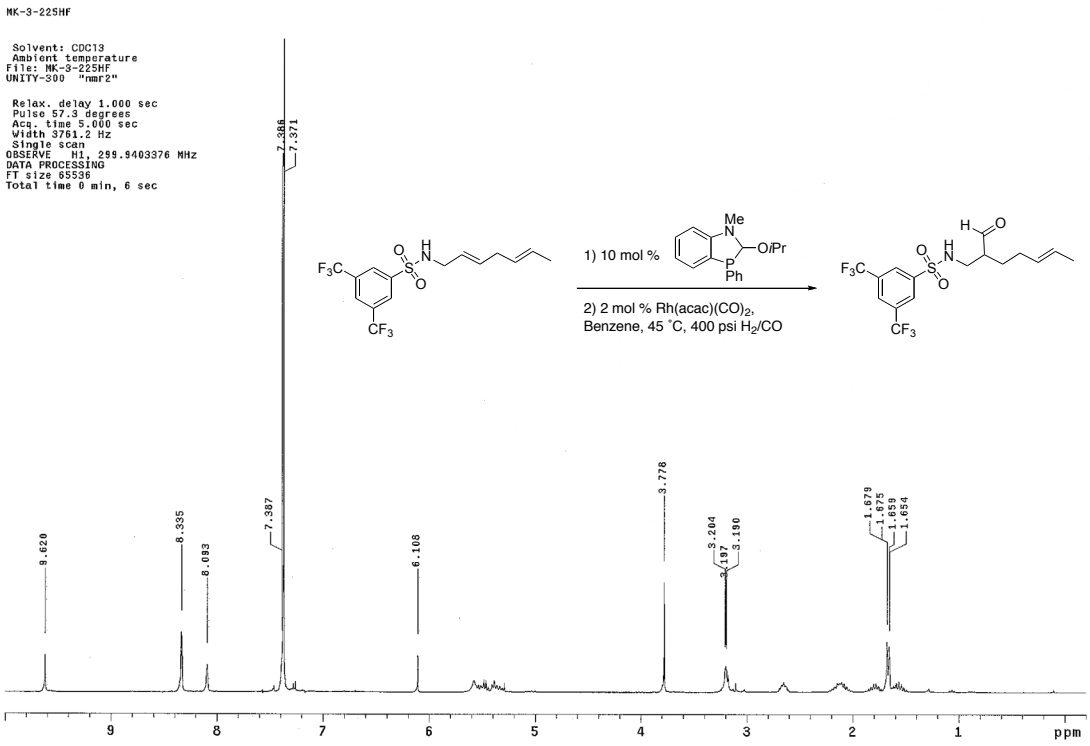


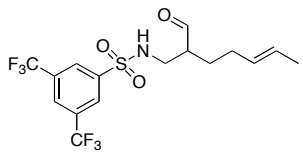
Cmpd. 2.30: 1-(3,5-Bis(trifluoromethyl)phenylsulfonyl)-3-(4-methoxyphenyl) pyrrolidin-2-ol

SFC (Silica, 5.0 mL/min, 1.0% MeOH, 220 nm, 150 bar, 50 ˚C) t_r = 4.3 and 5.2 min (diastereomers); **^{1}H NMR** (Acetone *d*-6, 400 MHz, 1:1 diastereomer ratio) δ 8.55 (s, 0.5H), 8.46 (s, 2.0H), 8.33-8.44 (m, 2.3H), 7.23 (d, 0.7H, J = 8.2), 7.15 (d, 2.2H, J = 8.4), 6.80-6.87 (m, 3.3H), 5.62-5.67 (m, 1.2H), 5.50 (dd, 1.2H, J = 3.1, 6.0), 5.17 (d, 0.3H, J = 6.4), 3.77 (s, 4.5H), 3.66-3.75 (m, 2.0H), 3.46-3.58 (m, 2.3H), 3.27 (dt, 1.9H, J = 2.8, 6.6), 2.35-2.49 (m, 2.1H), 2.07-2.15 (m, 2.1H)**; ^{13}C NMR** (Acetone *d*-6, 100 MHz) δ 160.2, 144.9, 133.2 (q, J = 33.7), 133.2 (q, J = 33.7), 131.4, 130.8, 129.8, 129.5, 129.5 (q, J = 272.0), 129.1, 127.6, 115.5, 114.9, 91.9, 86.5, 56.1, 53.7, 50.8, 48.1, 47.4, 28.8; **IR**: 3495, 3088, 2959, 2841, 1724, 1613, 1515, 1459, 1359, 1279, 1251, 1163, 1136, 1035, 906, 843, 699, 682, 640, 594 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{17}F_6NO_4SNa$ $[M+Na]^+$: 492.0680, found: 492.0690.

Table 4, Entry 4:

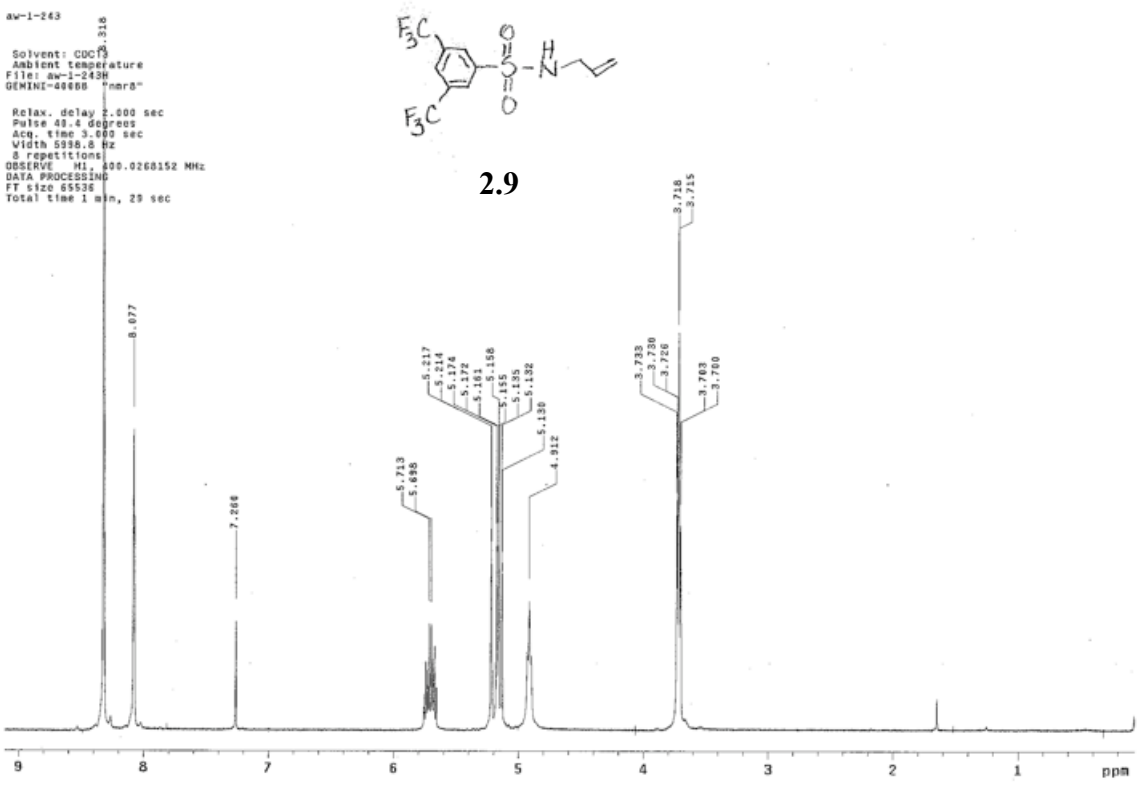
N-((2*E*,5*E*)-Hepta-2,5-dienyl)-3,5-bis(trifluoromethyl)benzenesulfonamide was hydroformylated using the corresponding General Procedure D. Analysis of the crude reaction mixture by ^{1}H NMR showed conversion and selectivity. A mixture of normal and iso products was isolated as a white solid (63.4 mg, 76%) with selectivity determined by NMR to be >95:5.





Cmpd. 2.26: (*E*)-*N*-(2-Formylhept-5-enyl)-3,5-bis(trifluoromethyl) benzenesulfonamide. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.62 (s, 1H), 8.31 (s, 2H), 8.08 (s,

1H), 5.20-5.60 (m, 2H), 3.09-3.22 (m, 2H), 2.62-2.64 (m, 1H), 2.07-2.20 (m, 2H), 1.67-1.9 (m, 1H), 1.65 (d, 3H, J = 5.99), 1.53-1.60 (m, 2H)**;** ^{13}**C NMR** ($CDCl_3$, 100 MHz) δ 203.9, 143.2, 133.2 (q, J = 34.5), 129.0, 128.2, 127.6, 126.4, 122.6. (q, J = 272.8), 51.0, 41.4, 29.8, 26.1, 18.0; **IR**: 3295, 3087, 3936, 2859, 1721, 1625, 1453, 1359, 1278, 1138, 969, 906, 844, 699, 682, 630 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{16}H_{18}F_6NO_3S$ $[M+H]^+$: 418.0912, found: 418.0898.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Width 5998.8 Hz
8 repetitions
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Total time 1 min, 29 sec
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8.077
7.264
5.713
5.698
5.217
5.214
5.174
5.172
5.161
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3.718
3.715
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7
6
5
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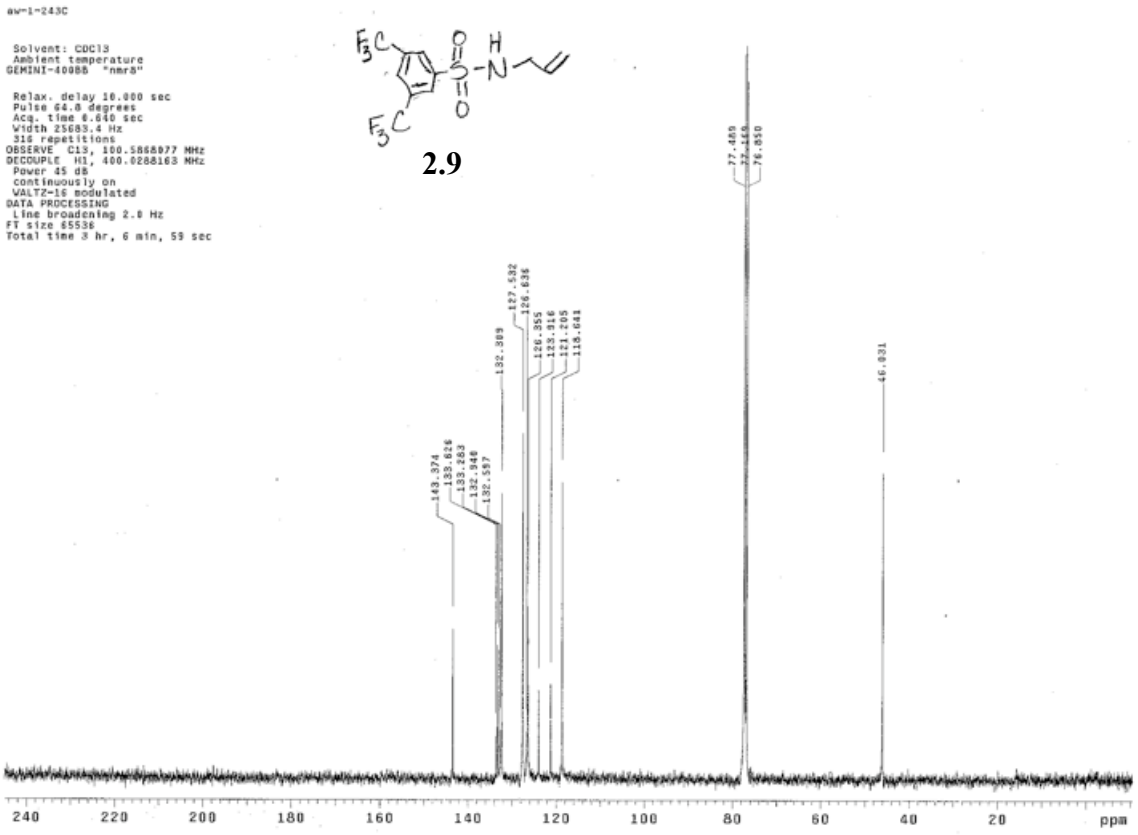
1
ppm

2.9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Ambient temperature
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Pulse 64.0 degrees
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DECOUPLE H1, 400.0288163 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.8 Hz
FT size 65536
Total time 3 hr, 6 min, 59 sec
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133.263
132.948
132.597
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20
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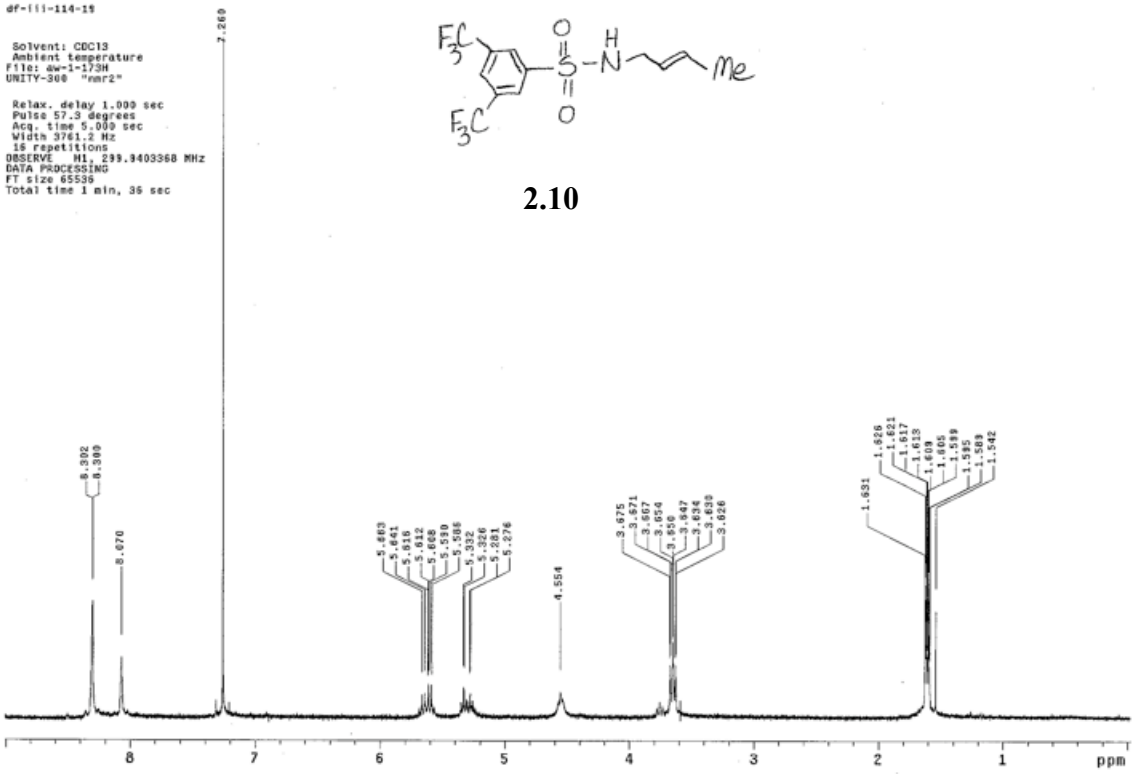
2.9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Ambient temperature
File: aw-1-173H
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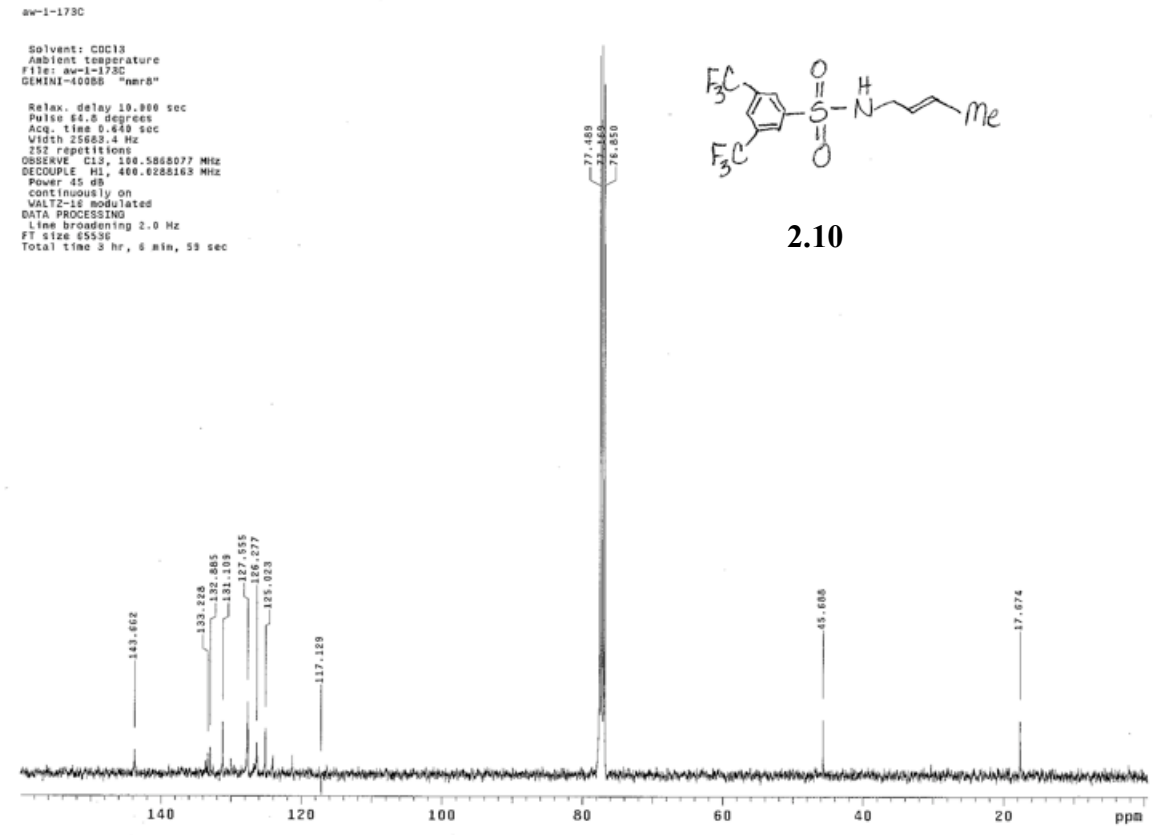
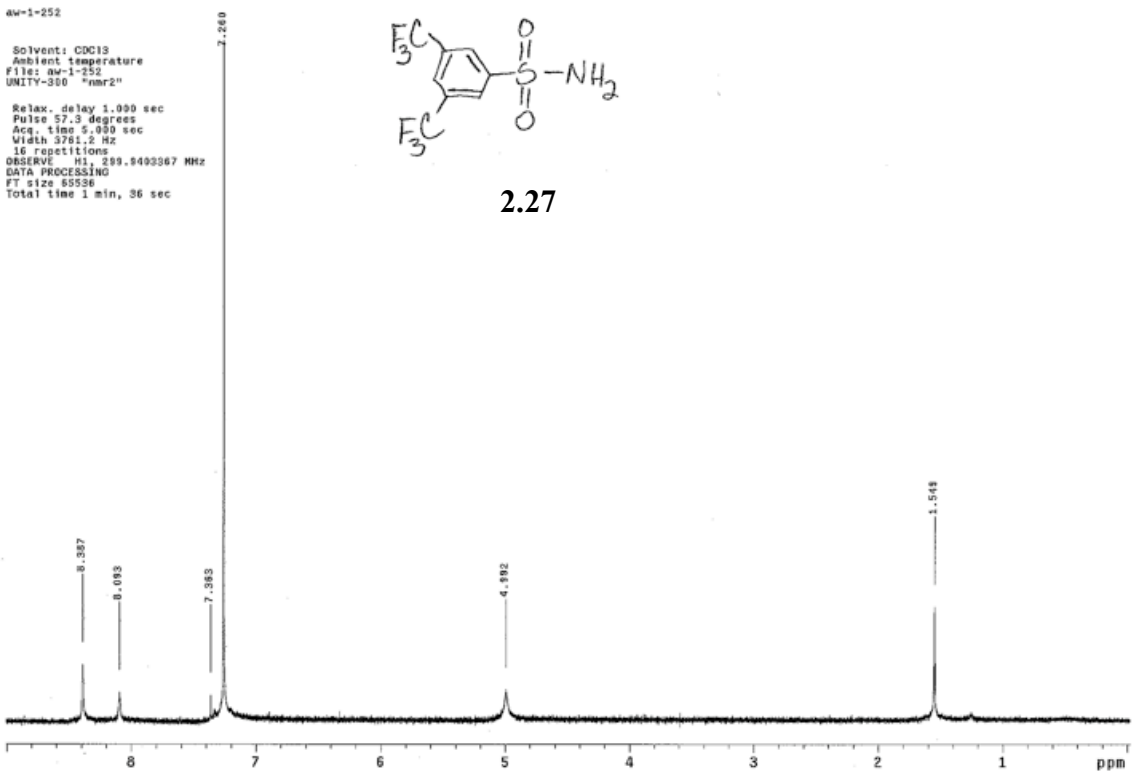
Relax. delay 1.000 sec
Pulse 57.3 degrees
Acq. time 5.000 sec
Width 3761.2 Hz
16 repetitions
OBSERVE H1, 299.9403368 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 36 sec
7.269
8.392
8.369
8.670
5.663
5.641
5.618
5.612
5.588
5.530
5.506
5.332
5.326
5.281
5.276
4.554
3.675
3.671
3.667
3.654
3.650
3.647
3.634
3.630
3.626
1.631
1.626
1.621
1.617
1.613
1.609
1.605
1.599
1.595
1.589
1.542
8
7
6
5
4
3
2
1
ppm

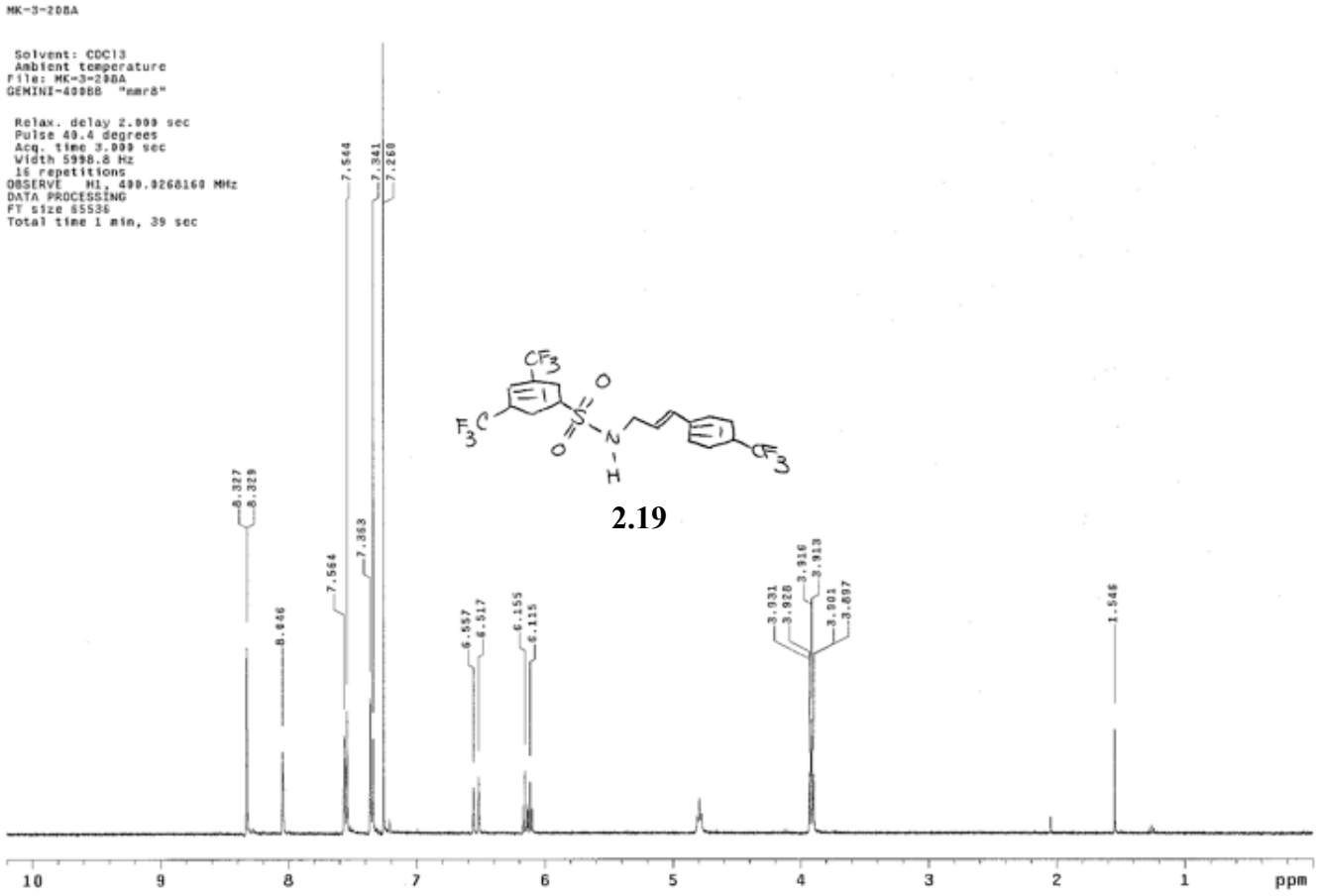
2.10


aw-1-173C
Solvent: CDCl3
Ambient temperature
File: aw-1-173C
GEMINI-400BB "nmr8"
Relax. delay 10.000 sec
Pulse 64.8 degrees
Acq. time 0.640 sec
Width 25683.4 Hz
252 repetitions
OBSERVE C13, 100.5868077 MHz
DECOUPLE H1, 400.0288163 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 3 hr, 6 min, 59 sec
77.489
77.168
76.850
143.662
133.228
132.885
131.109
127.555
126.277
125.023
117.129
45.686
17.674
140
120
100
80
60
40
20
ppm

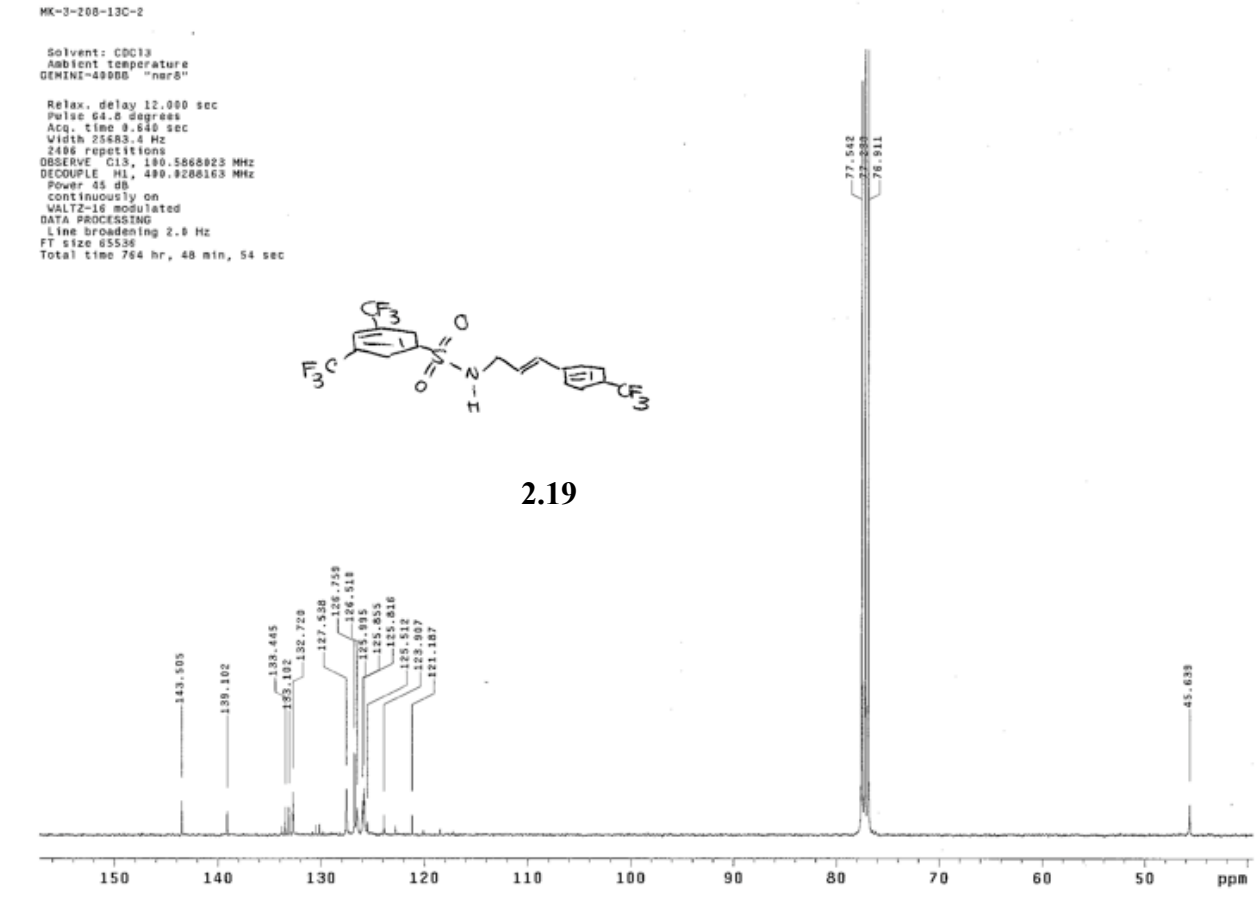
2.10


aw-1-252
Solvent: CDCl3
Ambient temperature
File: aw-1-252
UNITY-300 "nmr2"
Relax. delay 1.000 sec
Pulse 57.3 degrees
Acq. time 5.000 sec
Width 3761.2 Hz
16 repetitions
OBSERVE H1, 299.9403367 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 36 sec
7.260
8.387
8.093
7.383
4.992
1.548
8
7
6
5
4
3
2
1
ppm

2.27


MK-3-208A
Solvent: CDCl3
Ambient temperature
File: MK-3-208A
GEMINI-400BB "nmr8"
Relax. delay 2.000 sec
Pulse 40.4 degrees
Acq. time 3.000 sec
Width 5998.8 Hz
16 repetitions
OBSERVE H1, 400.9268160 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 39 sec
7.544
7.341
7.260
8.327
8.329
8.046
7.564
7.383
6.557
6.517
6.155
6.115
3.931
3.926
3.916
3.913
3.901
3.897
1.546
10
9
8
7
6
5
4
3
2
1
ppm

2.19

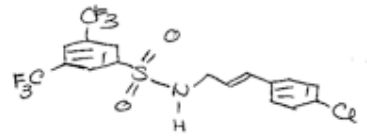

MK-3-208-13C-2
Solvent: CDCl3
Ambient temperature
GEMINI-400BB "nmr8"
Relax. delay 12.000 sec
Pulse 64.8 degrees
Acq. time 0.640 sec
Width 25683.4 Hz
2406 repetitions
OBSERVE C13, 100.5868023 MHz
DECOUPLE H1, 400.9288163 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 764 hr, 48 min, 54 sec
77.542
77.220
76.911
143.505
139.102
133.445
133.102
132.720
127.538
126.759
126.518
125.995
125.855
125.816
125.512
123.907
121.187
45.639
150
140
130
120
110
100
90
80
70
60
50
ppm

2.19

217
~~MK-3-226crystal~~

Solvent: CDCl3
Ambient temperature
File: MK-3-226crystal
UNITY-300 "nmr2"

Relax. delay 1.000 sec
Pulse 57.3 degrees
Acq. time 5.000 sec
Width 3761.2 Hz
16 repetitions
OBSERVE H1, 299.9403376 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 36 sec

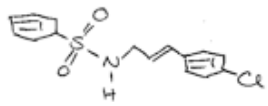


2.21

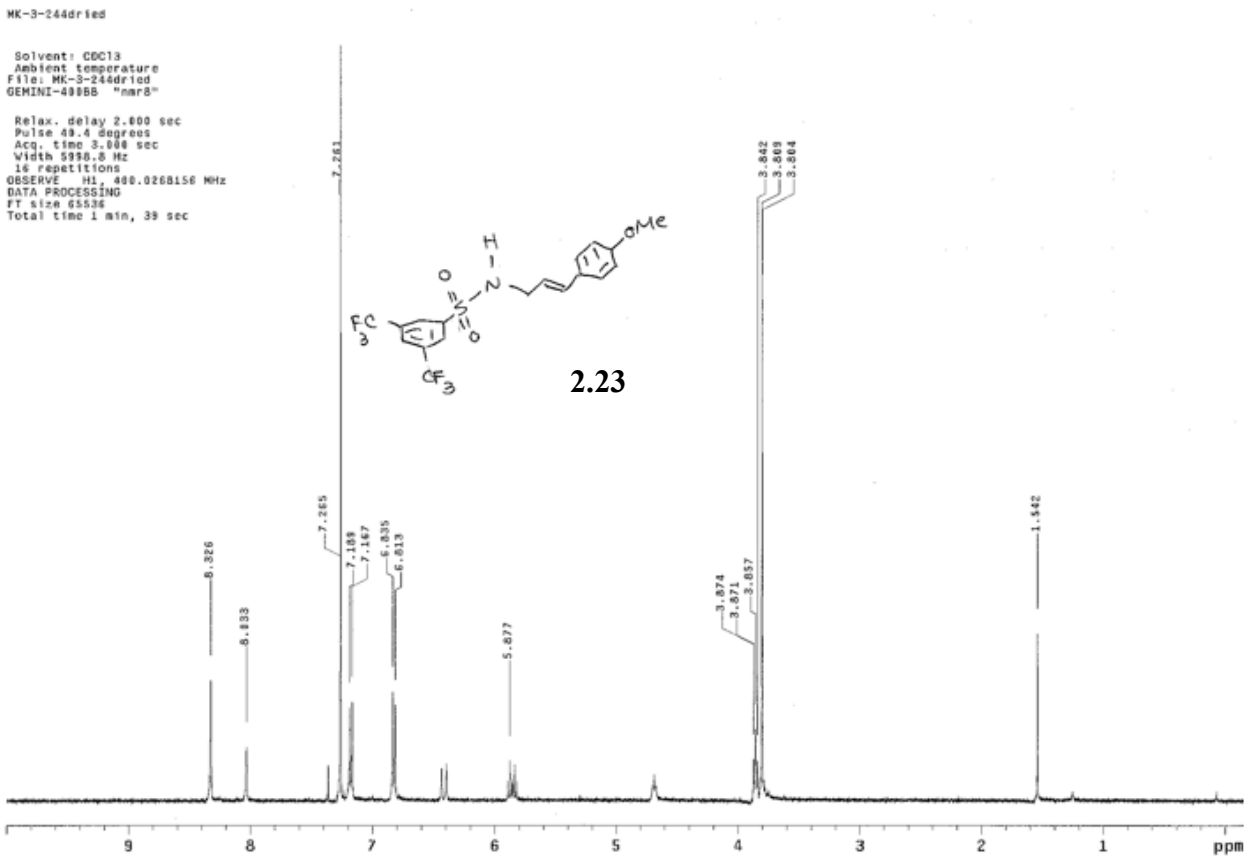
MK-3-209-13C

Solvent: CDCl3
Ambient temperature
File: MK-3-209-13C
GEMINI-400BB "nmr8"

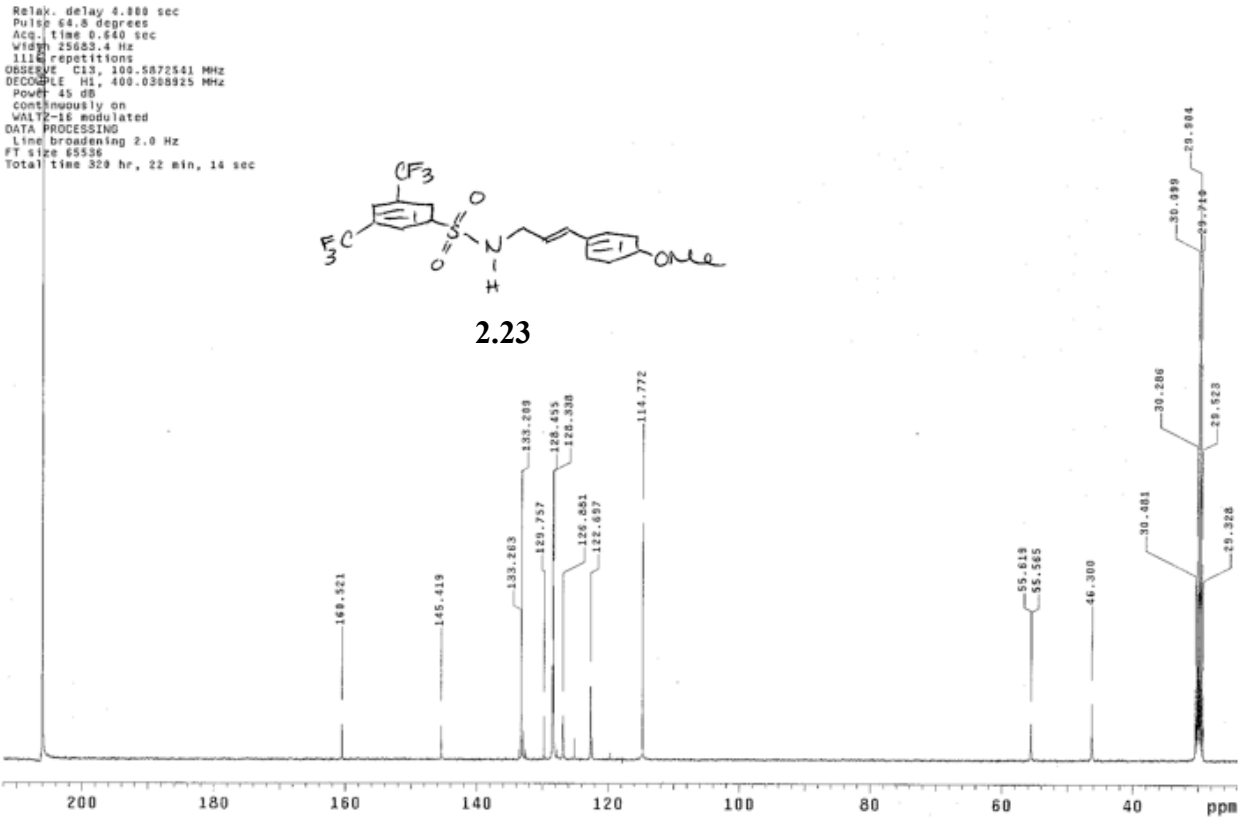
Relax. delay 12.000 sec
Pulse 64.8 degrees
Acq. time 0.640 sec
Width 25683.4 Hz
320 repetitions
OBSERVE C13, 100.5868031 MHz
DECOUPLE H1, 400.0288163 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 764 hr, 48 min, 54 sec



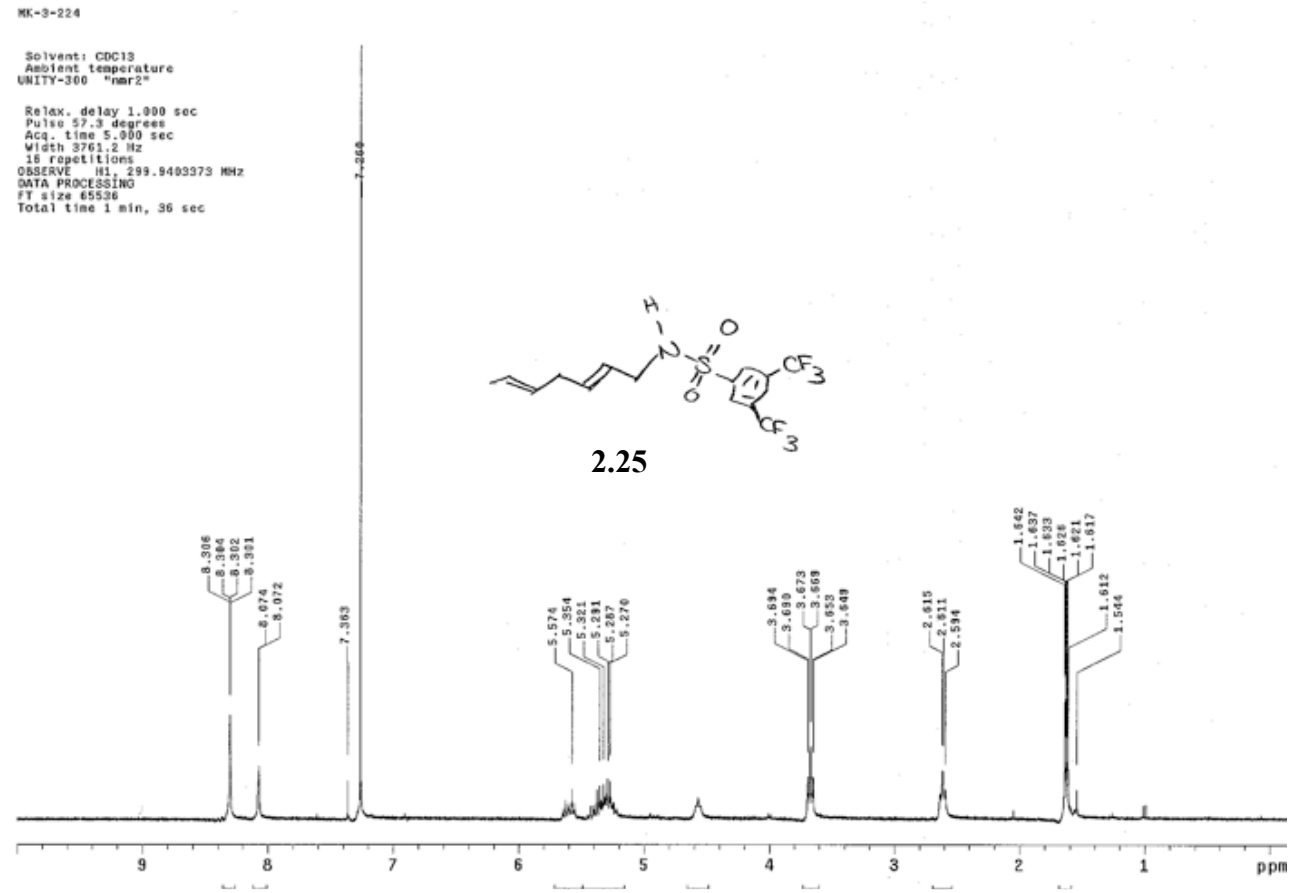
2.21


MK-3-244dried
Solvent: CDCl3
Ambient temperature
File: MK-3-244dried
GEMINI-400BB "nmr8"
Relax. delay 2.000 sec
Pulse 49.4 degrees
Acq. time 3.008 sec
Width 5998.8 Hz
16 repetitions
OBSERVE H1, 400.0268156 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 39 sec
7.261
3.842
3.869
3.864
8.326
8.833
7.265
7.189
7.167
6.835
6.813
5.877
3.874
3.871
3.857
1.642
9
8
7
6
5
4
3
2
1
ppm

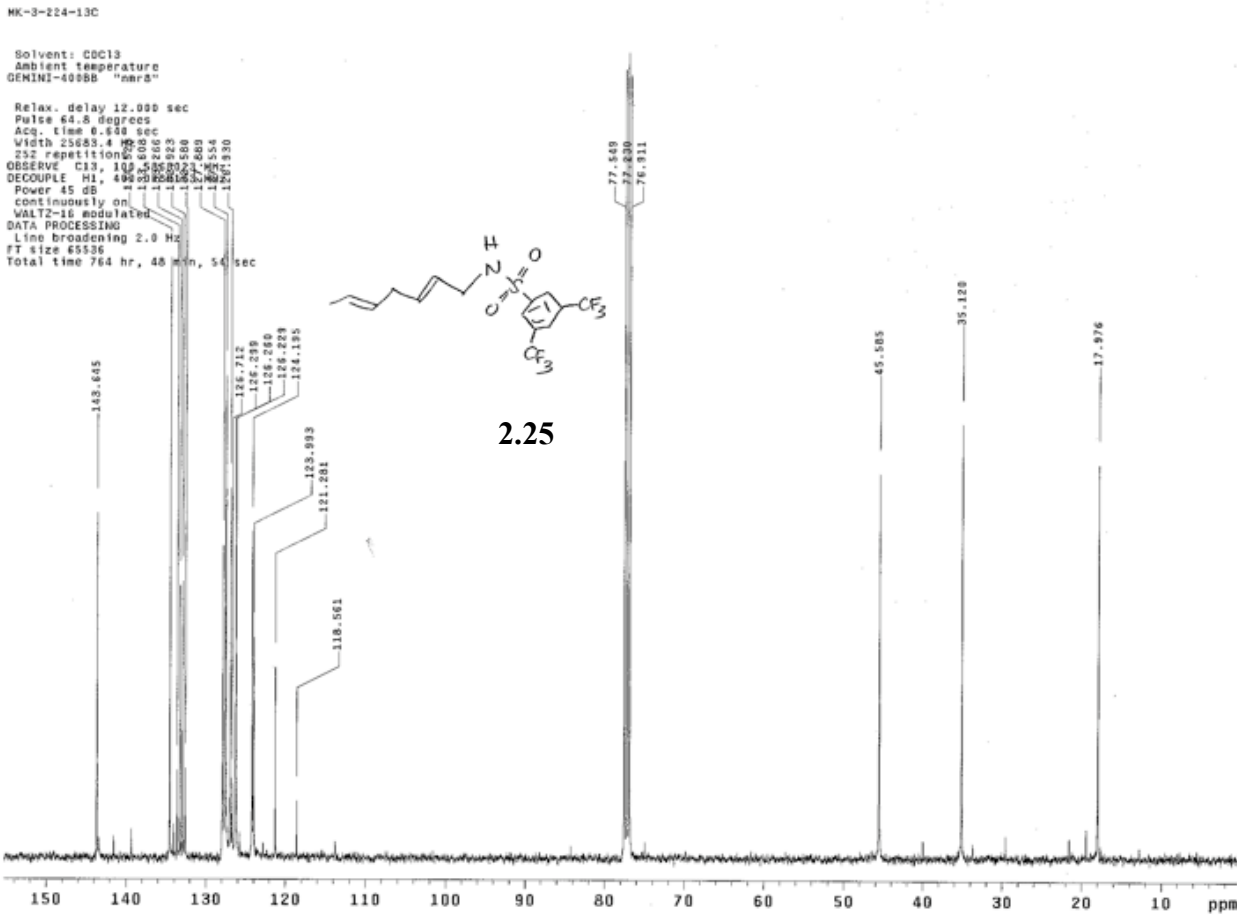
2.23


Relax. delay 4.888 sec
Pulse 64.8 degrees
Acq. time 0.640 sec
Width 25683.4 Hz
1116 repetitions
OBSERVE C13, 100.5872541 MHz
DECOUPLE H1, 400.0308925 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 329 hr, 22 min, 14 sec
160.521
145.419
133.263
133.209
129.757
128.455
128.338
126.851
122.697
114.772
55.619
55.565
46.300
30.481
30.286
30.099
29.904
29.710
29.523
29.328
200
180
160
140
120
100
80
60
40
ppm

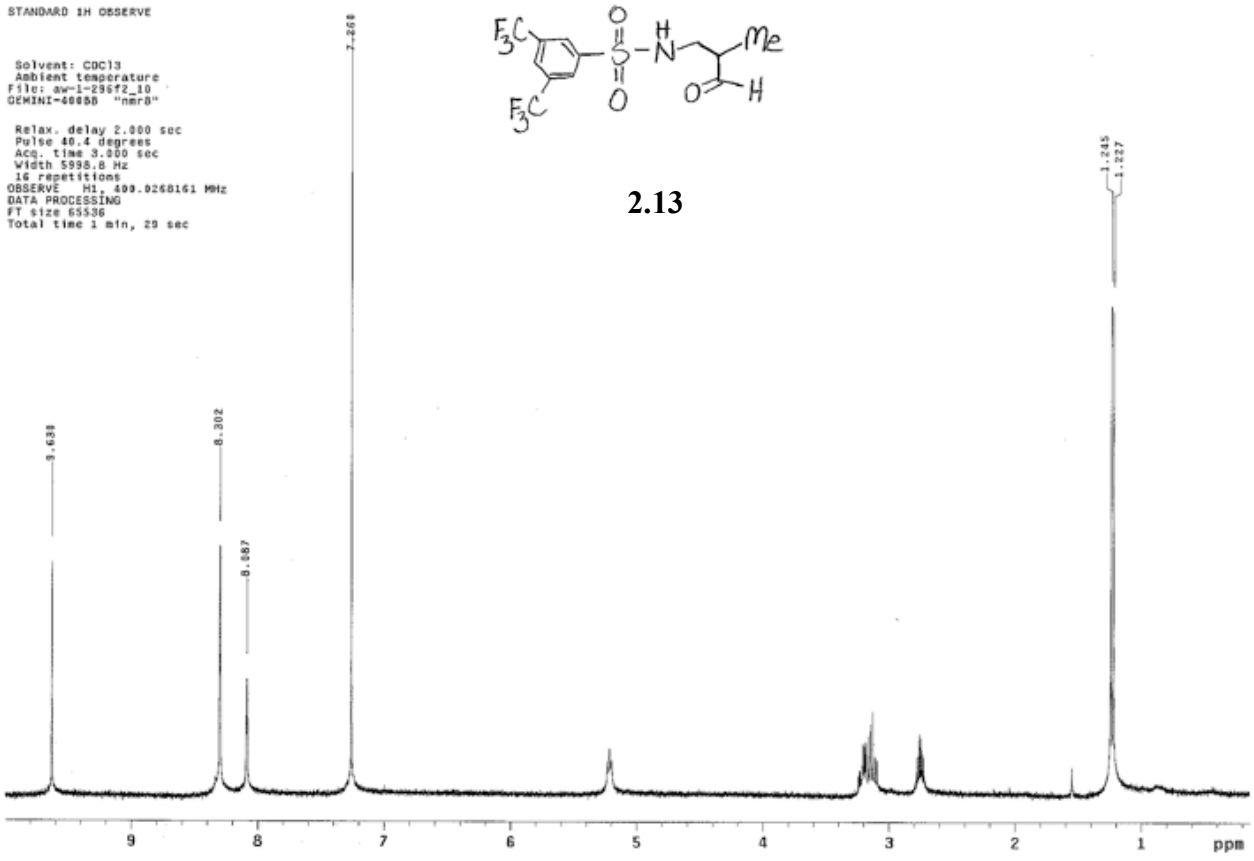
2.23


MK-3-224
Solvent: CDCl3
Ambient temperature
UNITY-300 "nmr2"
Relax. delay 1.000 sec
Pulse 57.3 degrees
Acq. time 5.000 sec
Width 3761.2 Hz
16 repetitions
OBSERVE H1, 299.9403373 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 36 sec
8.306
8.304
8.302
8.301
8.074
8.072
7.360
7.268
5.574
5.354
5.321
5.291
5.287
5.270
3.694
3.690
3.673
3.669
3.653
3.649
2.615
2.611
2.594
1.642
1.637
1.633
1.628
1.621
1.617
1.612
1.544
9
8
7
6
5
4
3
2
1
ppm

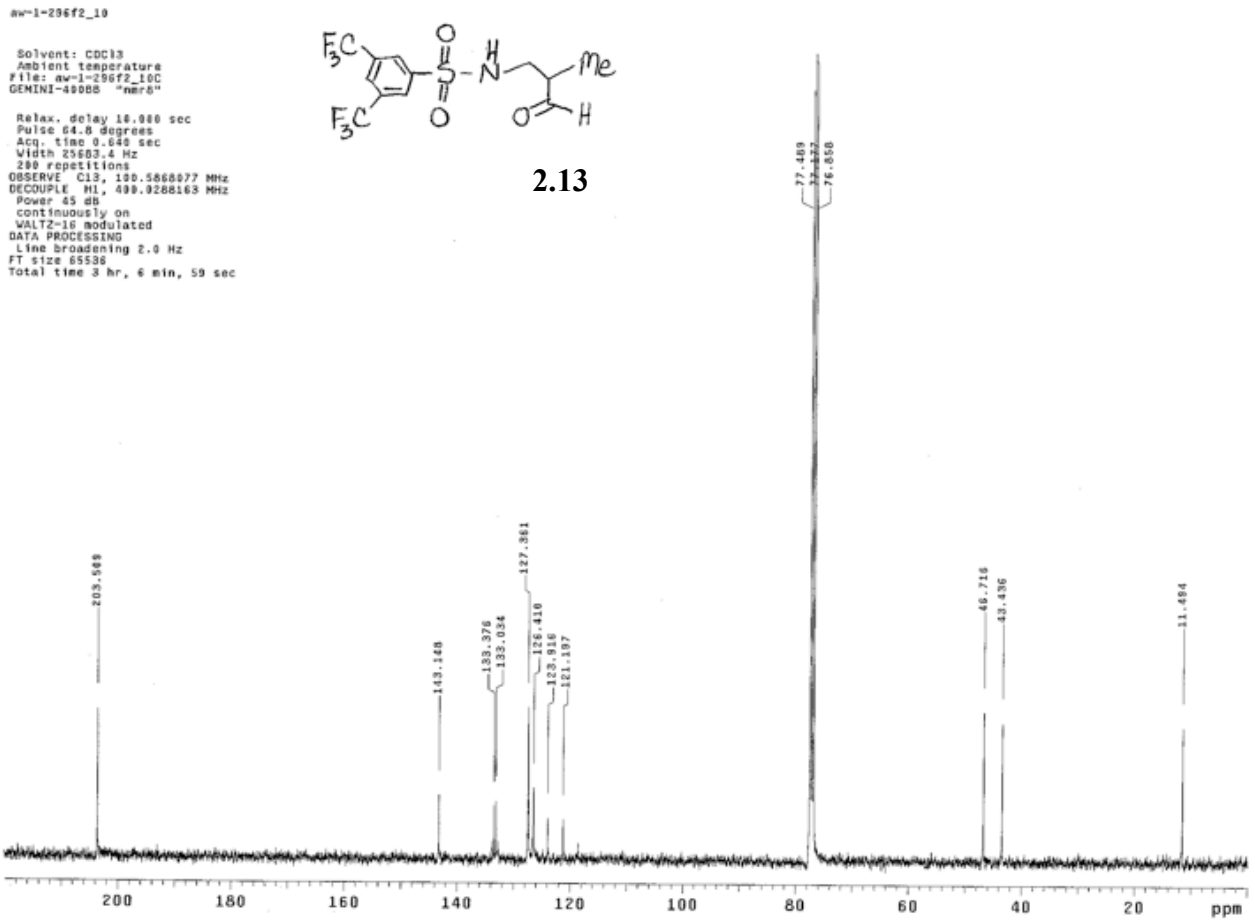
2.25


MK-3-224-13C
Solvent: CDCl3
Ambient temperature
GEMINI-400BB "nmr3"
Relax. delay 12.000 sec
Pulse 64.8 degrees
Acq. time 0.648 sec
Width 25683.4 Hz
252 repetitions
OBSERVE C13, 100.5
DECOUPLE H1, 400.1
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 764 hr, 48 min, 54 sec
148.645
126.712
126.249
126.200
126.229
124.195
123.893
121.281
118.561
77.549
77.230
76.911
45.585
35.128
17.976
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

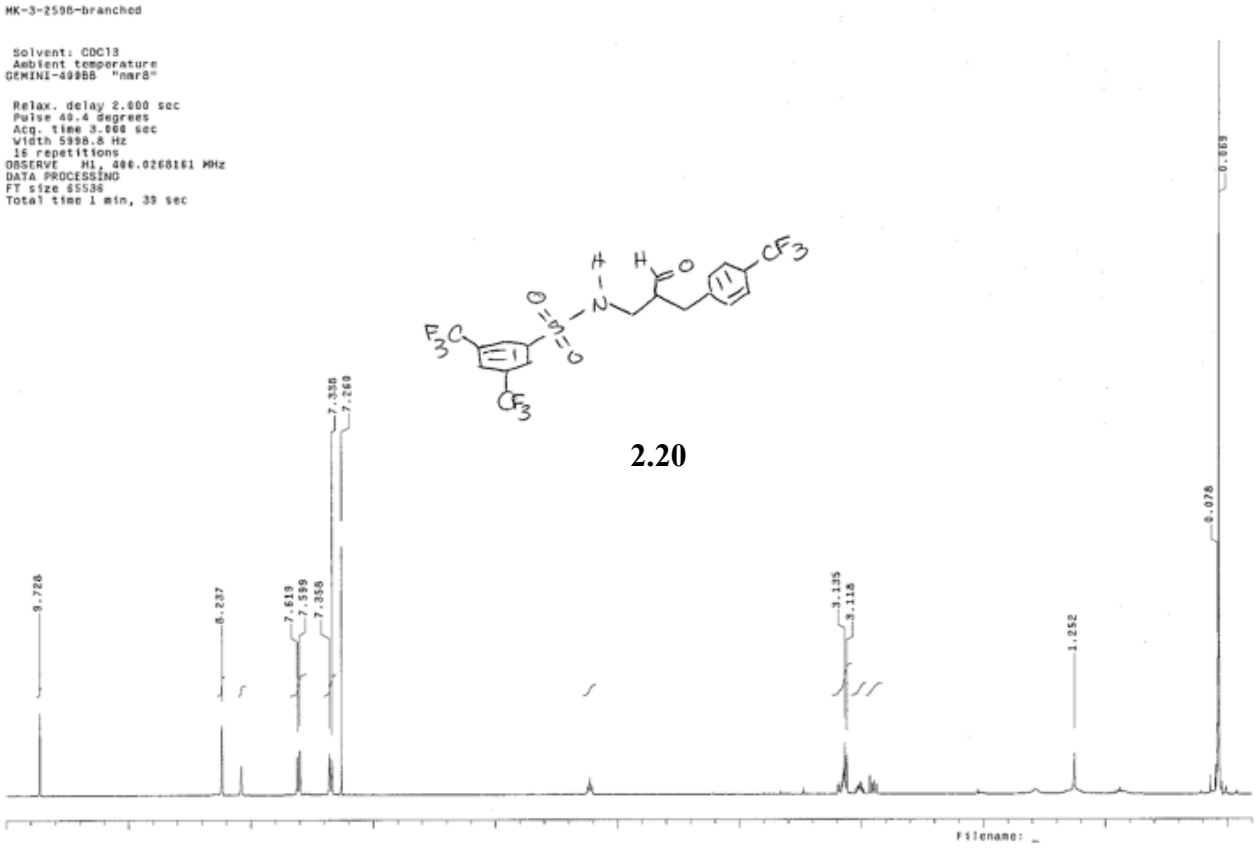
2.25


STANDARD 1H OBSERVE
Solvent: CDCl3
Ambient temperature
File: aw-1-296f2_10
GEMINI-400BB "nmr8"
Relax. delay 2.000 sec
Pulse 40.4 degrees
Acq. time 3.000 sec
Width 5998.8 Hz
16 repetitions
OBSERVE H1, 499.9268161 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 29 sec
9.638
8.302
8.087
7.268
1.245
1.227
ppm

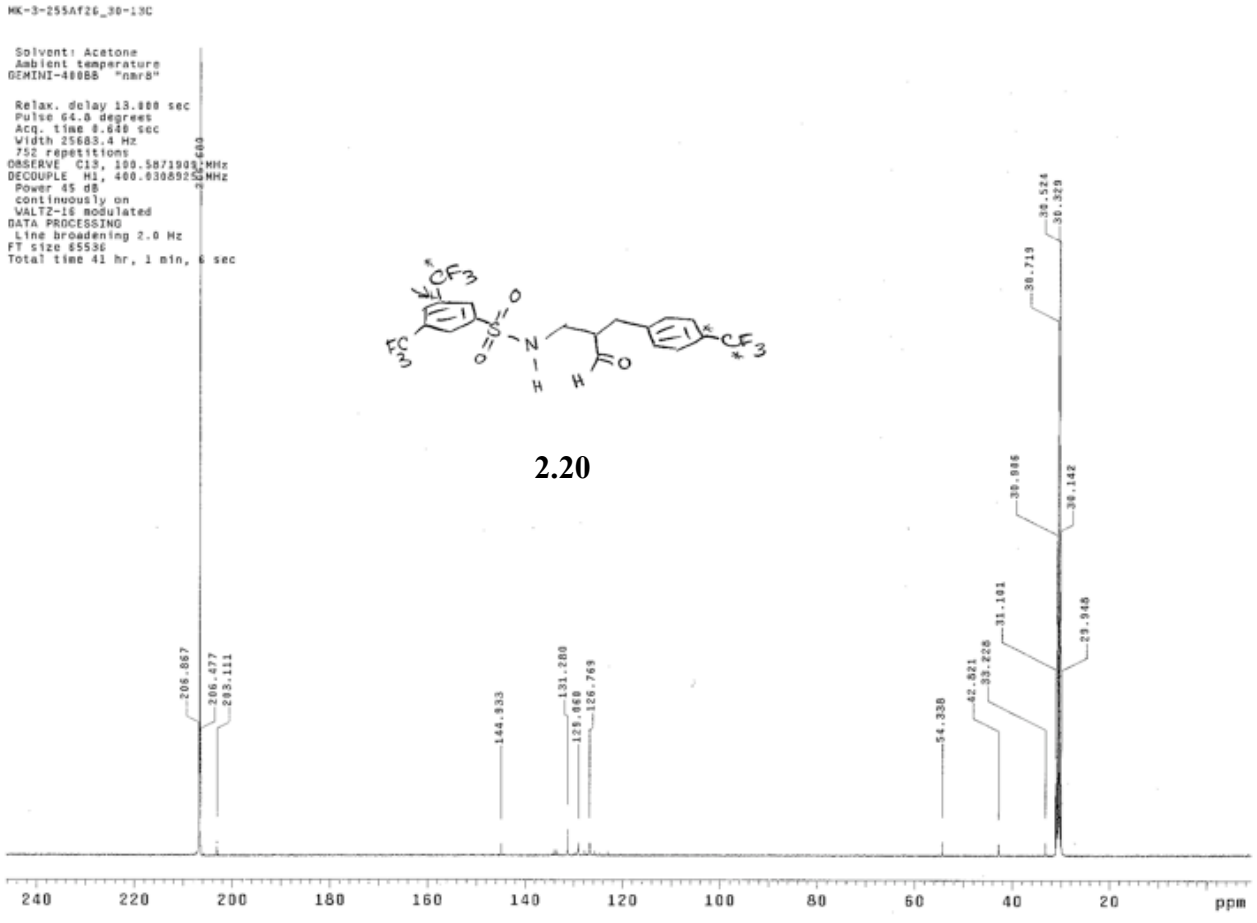
2.13


aw-1-296f2_10
Solvent: CDCl3
Ambient temperature
File: aw-1-296f2_10C
GEMINI-400BB "nmr8"
Relax. delay 10.000 sec
Pulse 64.8 degrees
Acq. time 0.840 sec
Width 25683.4 Hz
280 repetitions
OBSERVE C13, 100.5868077 MHz
DECOUPLE H1, 499.9288163 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 3 hr, 6 min, 59 sec
203.569
143.148
133.376
133.034
127.361
126.410
123.916
121.197
77.489
77.172
76.856
46.716
43.436
11.484
ppm

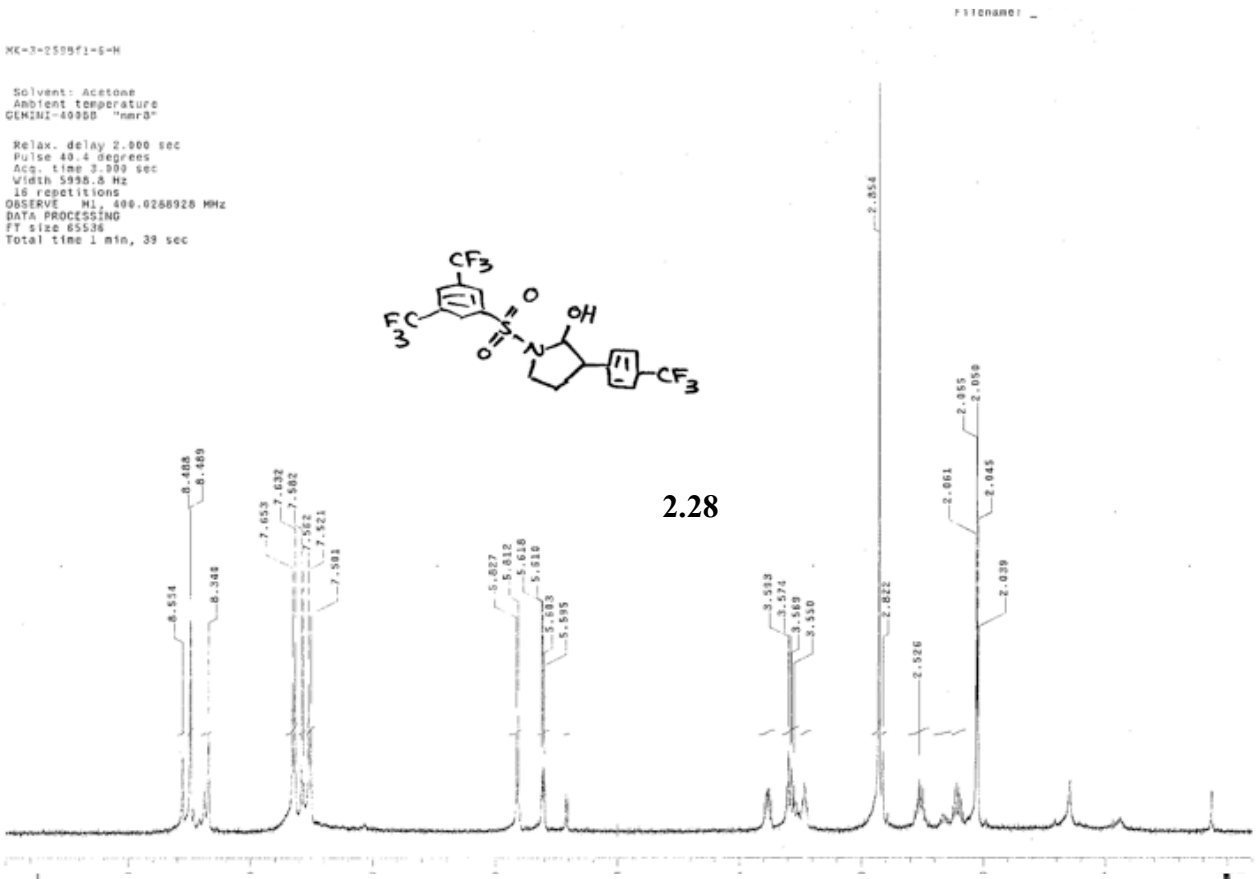
2.13


MK-3-259B-branched
Solvent: CDCl3
Ambient temperature
GEMINI-400BB "nmr8"
Relax. delay 2.000 sec
Pulse 40.4 degrees
Acq. time 3.868 sec
Width 5998.8 Hz
16 repetitions
OBSERVE H1, 400.0268161 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 39 sec
9.728
8.237
7.619
7.599
7.358
7.338
7.260
3.135
3.118
1.252
0.078
0.000
Filename:

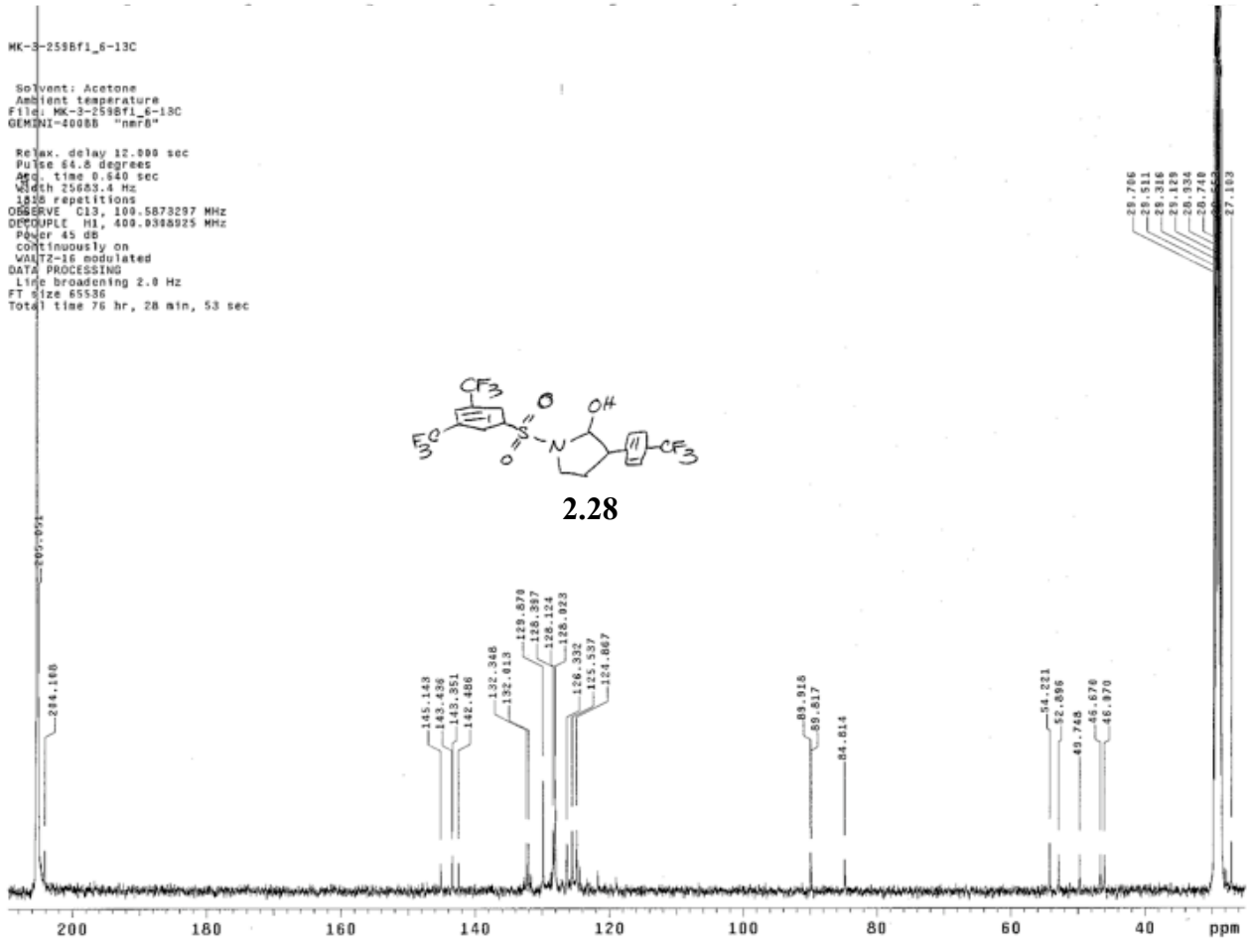
2.20


MK-3-255Af26_30-13C
Solvent: Acetone
Ambient temperature
GEMINI-400BB "nmr8"
Relax. delay 13.000 sec
Pulse 64.0 degrees
Acq. time 0.648 sec
Width 25683.4 Hz
752 repetitions
OBSERVE C13, 100.5871908 MHz
DECOUPLE H1, 400.6308925 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 41 hr, 1 min, 6 sec
206.867
206.477
205.111
144.833
131.280
125.868
126.769
54.338
42.821
33.228
31.161
30.886
30.142
29.948
30.719
30.524
30.329
240
220
200
180
160
140
120
100
80
60
40
20
ppm

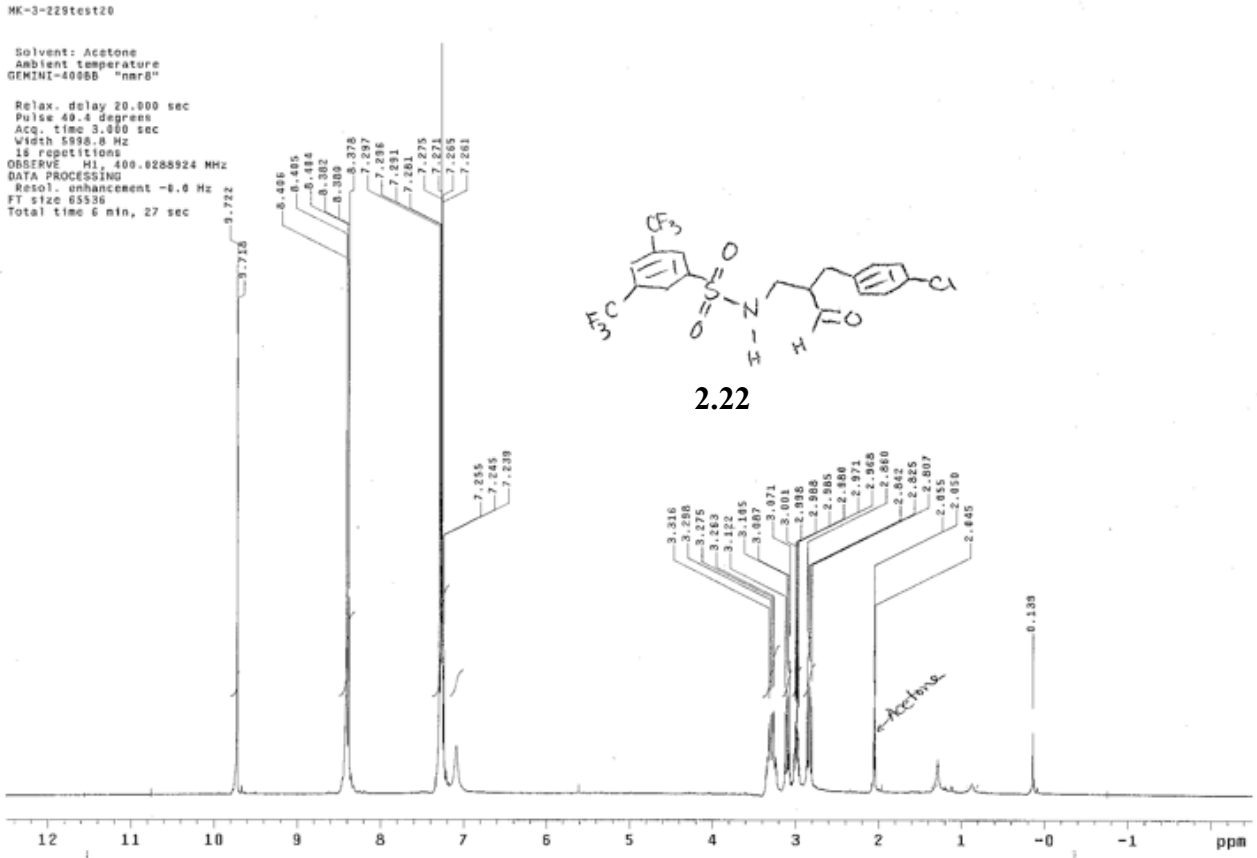
2.20


Filename: _
MK-3-259Bf1-6-H
Solvent: Acetone
Ambient temperature
GEMINI-400BB "nmr8"
Relax. delay 2.000 sec
Pulse 40.4 degrees
Acq. time 3.000 sec
Width 5998.8 Hz
16 repetitions
OBSERVE H1, 400.0268928 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 39 sec
8.488
8.469
8.554
8.348
7.653
7.632
7.582
7.562
7.521
7.501
5.827
5.812
5.618
5.610
5.585
5.565
3.593
3.574
3.569
3.550
2.854
2.822
2.661
2.655
2.059
2.045
2.039
2.526

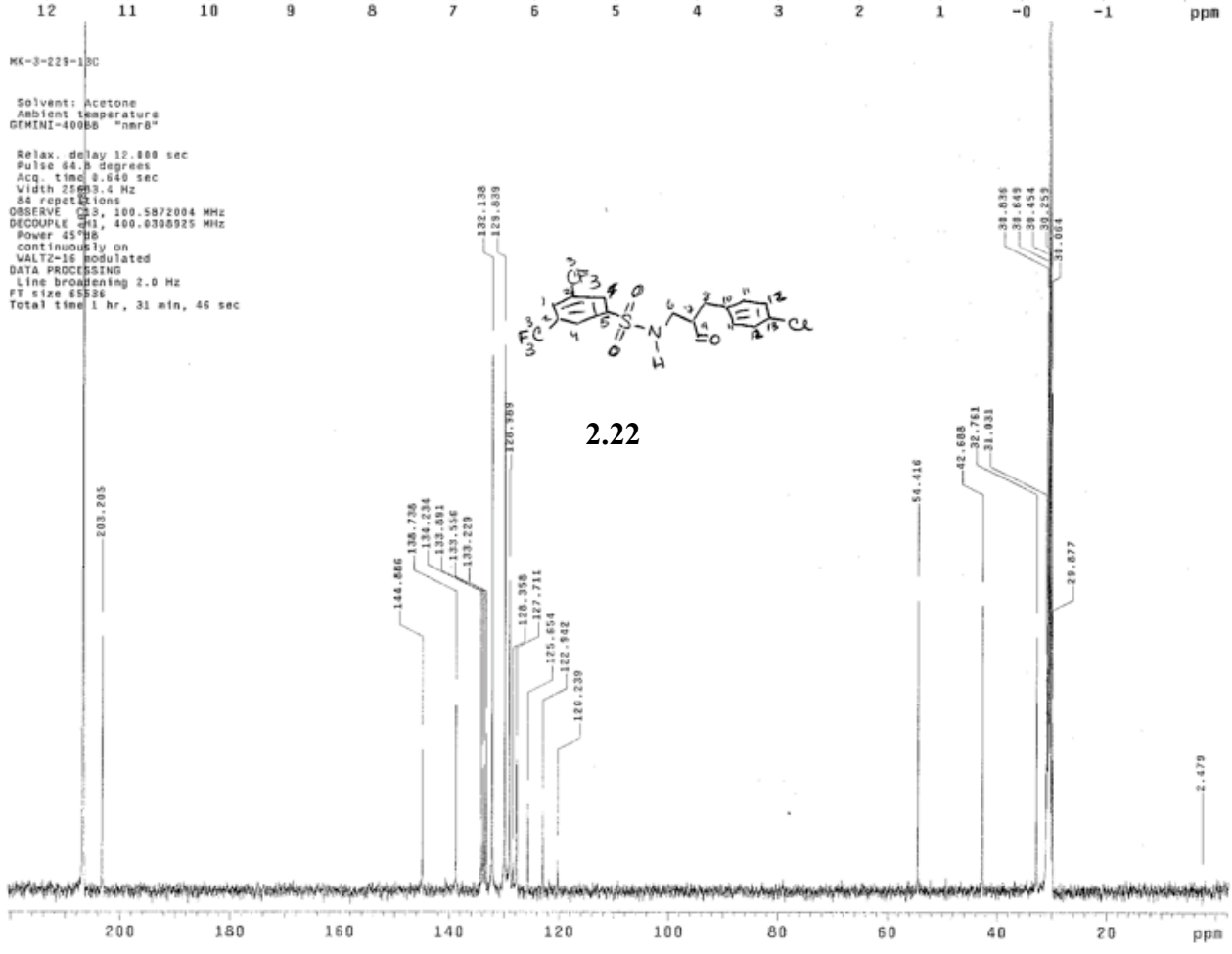
2.28


MK-3-259Bf1_6-13C
Solvent: Acetone
Ambient temperature
File: MK-3-259Bf1_6-13C
GEMINI-400BB "nmr8"
Relax. delay 12.000 sec
Pulse 64.8 degrees
Acq. time 0.640 sec
Width 25683.4 Hz
1808 repetitions
OBSERVE C13, 100.5873297 MHz
DECOUPLE H1, 400.0308925 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 76 hr, 28 min, 53 sec
200.091
184.160
145.143
143.436
143.351
142.486
132.348
132.013
129.879
128.397
128.124
128.023
126.332
125.537
124.867
89.918
89.817
84.614
54.221
52.856
49.748
46.670
46.870
28.706
28.511
28.316
28.129
28.334
28.748
28.553
27.103
200
180
160
140
120
100
80
60
40
ppm

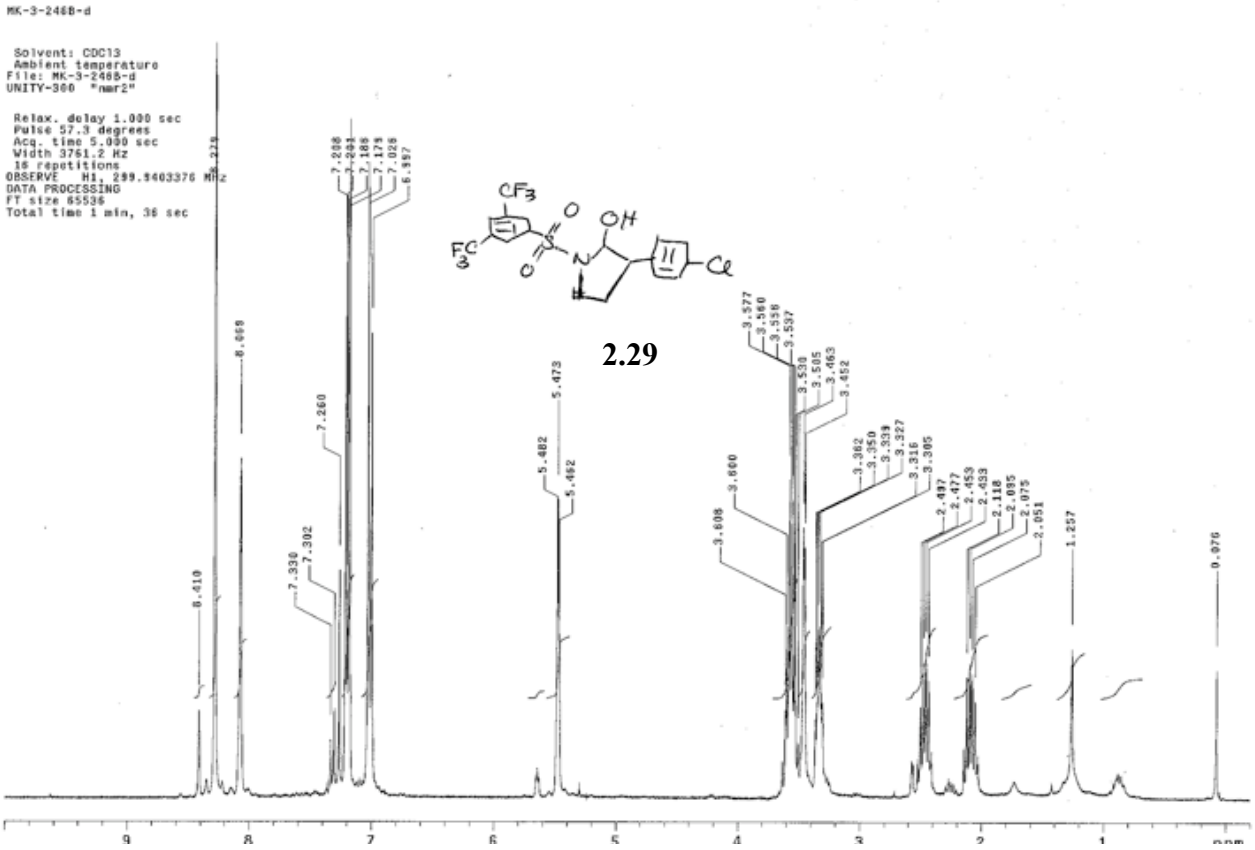
2.28

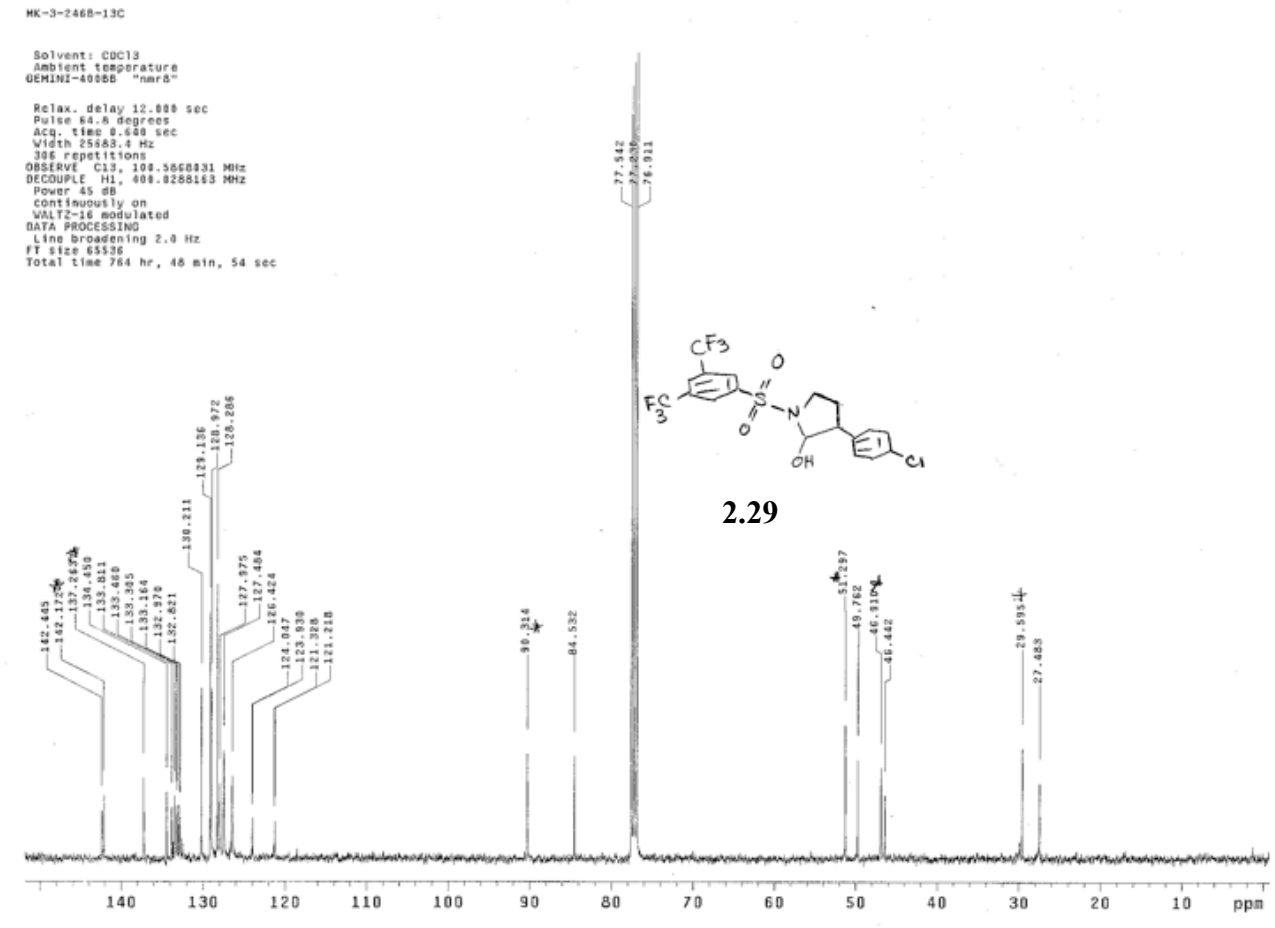

MK-3-229test20
Solvent: Acetone
Ambient temperature
GEMINI-400BB "nmr8"
Relax. delay 20.000 sec
Pulse 40.4 degrees
Acq. time 3.000 sec
Width 5998.8 Hz
16 repetitions
OBSERVE H1, 400.0288924 MHz
DATA PROCESSING
Resol. enhancement -0.6 Hz
FT size 65536
Total time 6 min, 27 sec
Acetone
ppm

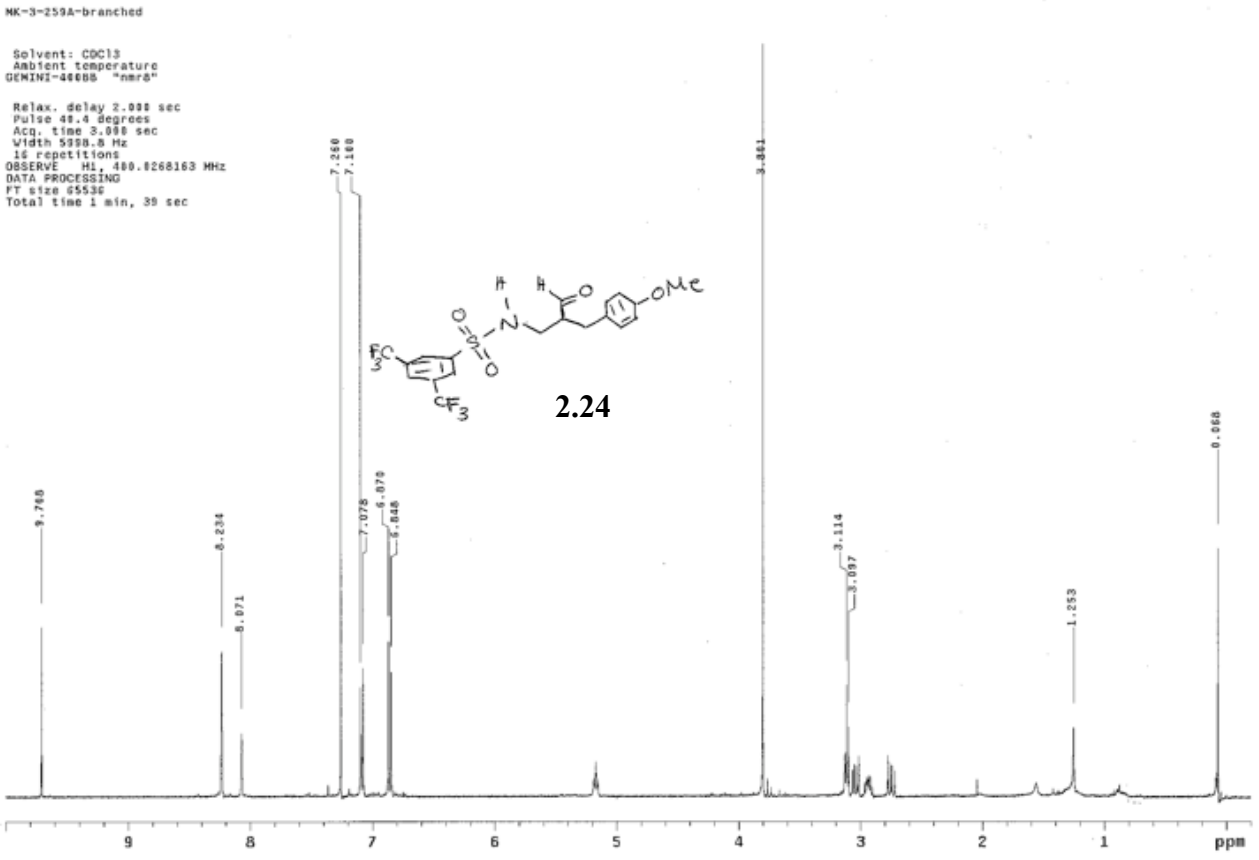
2.22


MK-3-229-13C
Solvent: Acetone
Ambient temperature
GEMINI-400BB "nmr8"
Relax. delay 12.800 sec
Pulse 64.8 degrees
Acq. time 0.640 sec
Width 25083.4 Hz
84 repetitions
OBSERVE C13, 100.5872004 MHz
DECOUPLE H1, 400.0308925 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 1 hr, 31 min, 46 sec
ppm

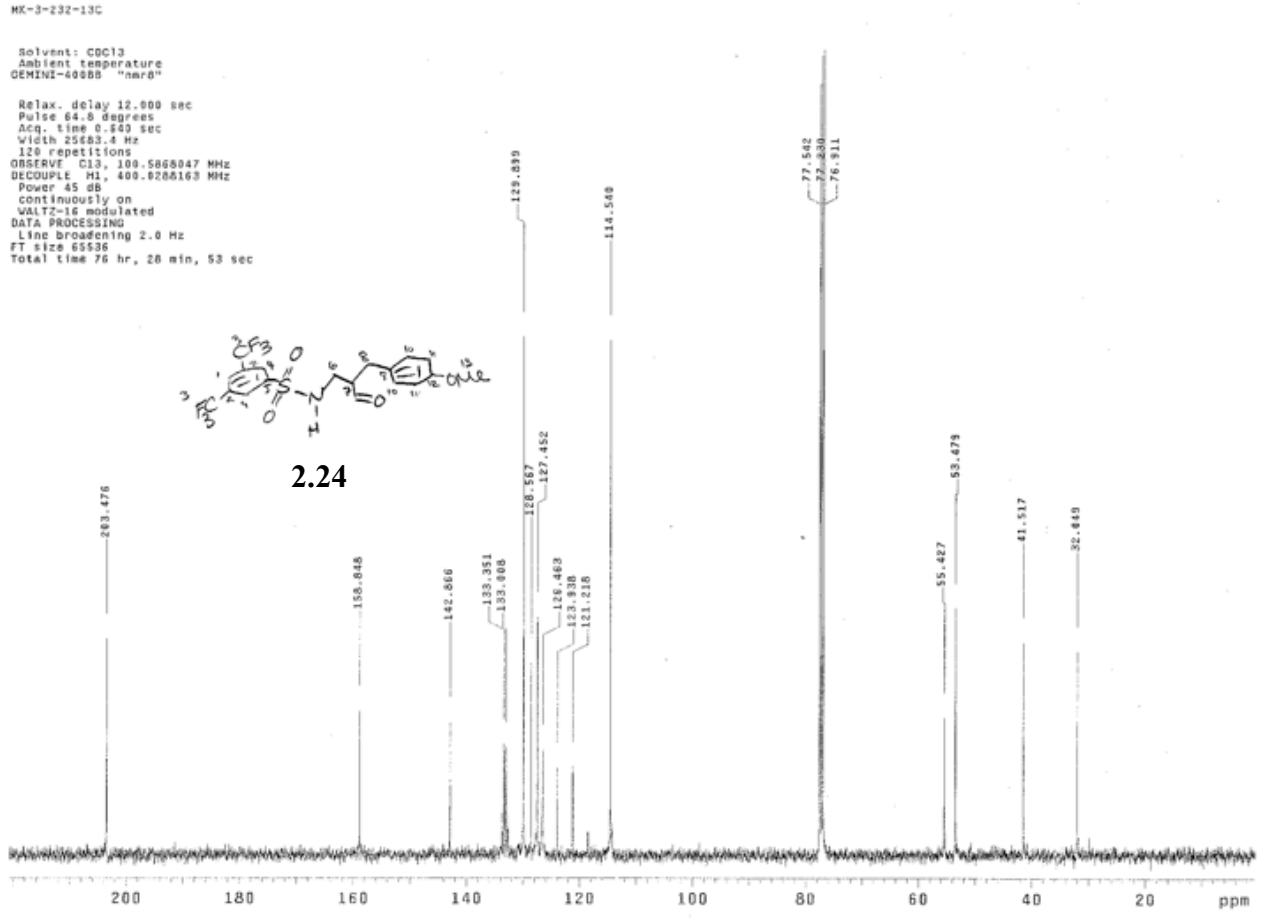
2.22


MK-3-246B-d
Solvent: CDCl3
Ambient temperature
File: MK-3-246B-d
UNITY-300 "nmr2"
Relax. delay 1.000 sec
Pulse 57.3 degrees
Acq. time 5.000 sec
Width 3761.2 Hz
16 repetitions
OBSERVE H1, 299.9403376 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 36 sec
CF3
FC3
O
OH
N
Cl
2.29


MK-3-246B-13C
Solvent: CDCl3
Ambient temperature
GEMINI-400BB "nmr8"
Relax. delay 12.000 sec
Pulse 64.6 degrees
Acq. time 0.600 sec
Width 25883.4 Hz
306 repetitions
OBSERVE C13, 100.5868831 MHz
DECOUPLE H1, 400.0288163 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 764 hr, 48 min, 54 sec
CF3
FC3
O
OH
N
Cl
2.29
ppm


MK-3-259A-branched
Solvent: CDCl3
Ambient temperature
GEMINI-400BB "nmr8"
Relax. delay 2.000 sec
Pulse 48.4 degrees
Acq. time 3.000 sec
Width 5998.8 Hz
16 repetitions
OBSERVE H1, 400.8268163 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 39 sec
9.708
8.234
8.071
7.260
7.160
7.078
6.870
6.848
3.861
3.114
3.057
1.253
0.068
ppm

2.24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Acq. time 0.540 sec
Width 25883.4 Hz
120 repetitions
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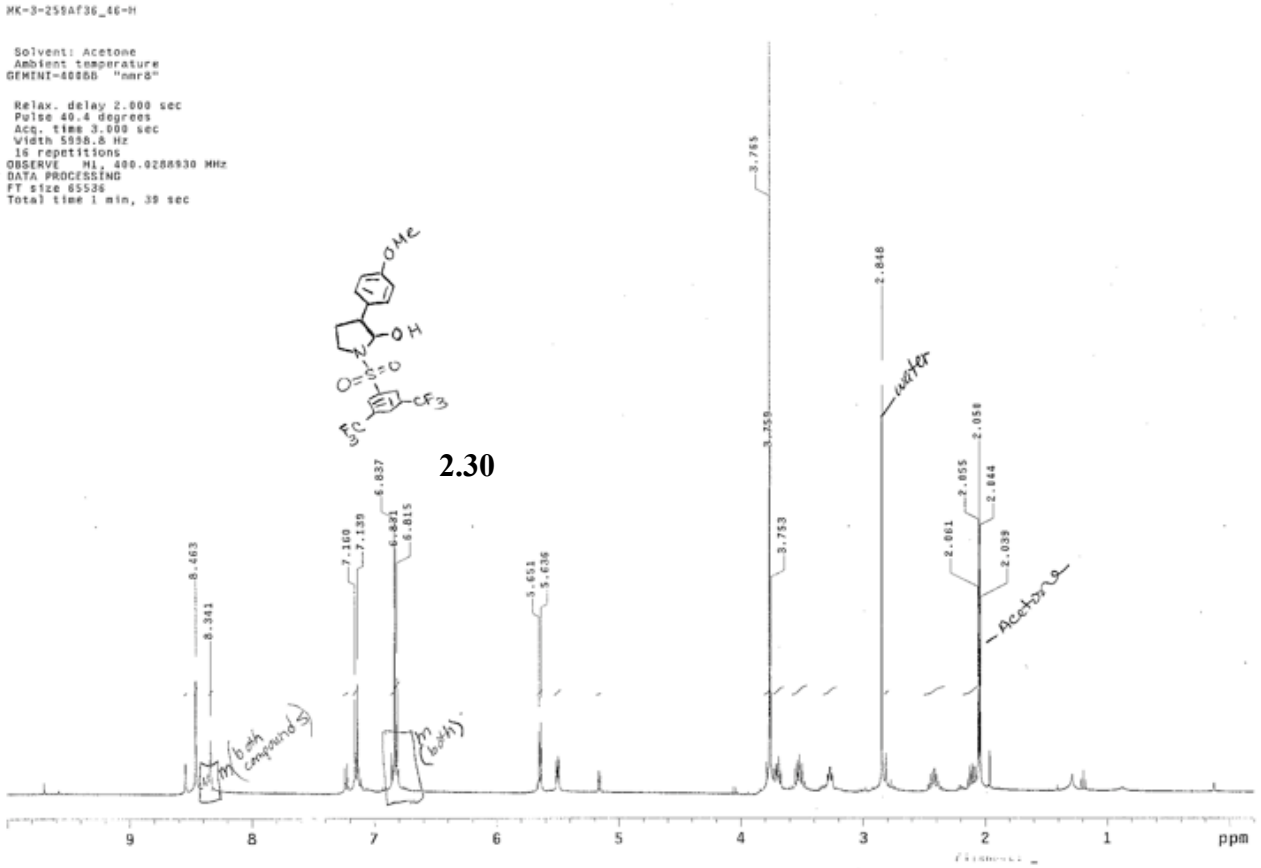
DECOUPLE H1, 400.8268163 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 76 hr, 28 min, 53 sec
203.476
158.848
142.866
133.351
133.008
129.039
128.567
127.452
126.463
123.938
121.218
114.540
77.542
77.230
76.911
55.427
53.479
41.517
32.649
ppm

2.24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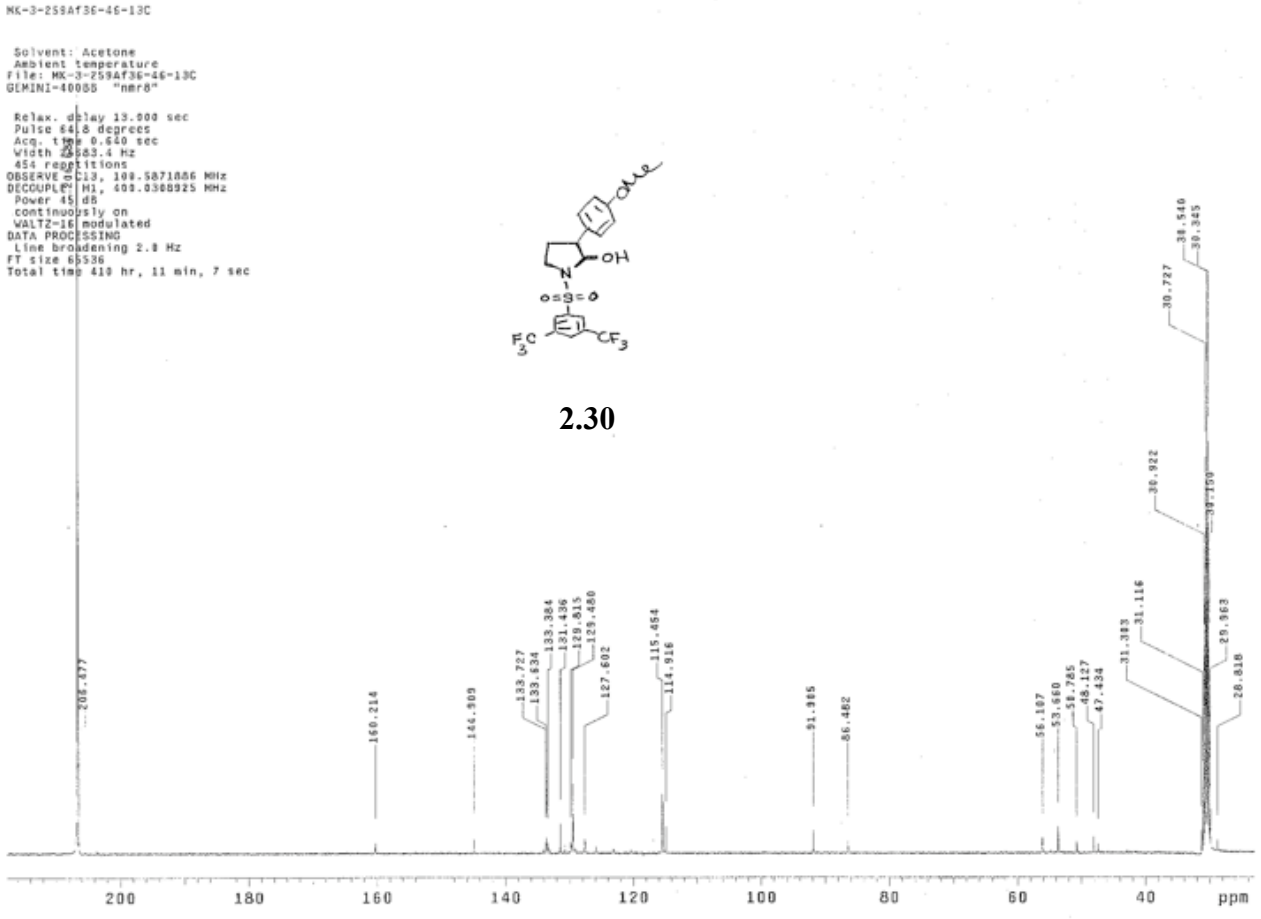
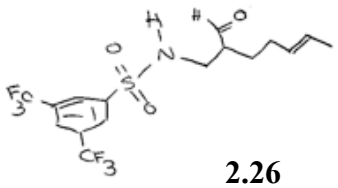
Ambient temperature
GEMINI-400BB "nmr8"
Relax. delay 2.000 sec
Pulse 40.4 degrees
Acq. time 3.000 sec
Width 5598.8 Hz
16 repetitions
OBSERVE H1, 400.0288930 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 39 sec
OMe
OH
O=S=O
CF3
F3C
2.30
8.463
8.341
7.160
7.139
6.837
6.821
6.815
5.651
5.636
3.765
3.759
3.753
2.848
water
2.061
2.055
2.044
2.039
Acetone
m (both compounds)
m (both)
9
8
7
6
5
4
3
2
1
ppm


MK-3-259Af36-46-13C
Solvent: Acetone
Ambient temperature
File: MK-3-259Af36-46-13C
GEMINI-400BB "nmr8"
Relax. delay 13.000 sec
Pulse 64.8 degrees
Acq. time 0.640 sec
Width 25583.4 Hz
454 repetitions
OBSERVE C13, 100.5871886 MHz
DECOUPLE H1, 400.0388925 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.8 Hz
FT size 65536
Total time 410 hr, 11 min, 7 sec
OMe
OH
O=S=O
CF3
F3C
2.30
208.477
160.214
144.909
133.727
133.634
133.384
131.436
129.815
129.480
127.602
115.454
114.916
91.985
66.462
56.107
53.660
50.785
48.127
47.434
38.540
38.345
30.727
30.922
30.750
31.383
31.116
29.963
28.618
200
180
160
140
120
100
80
60
40
ppm

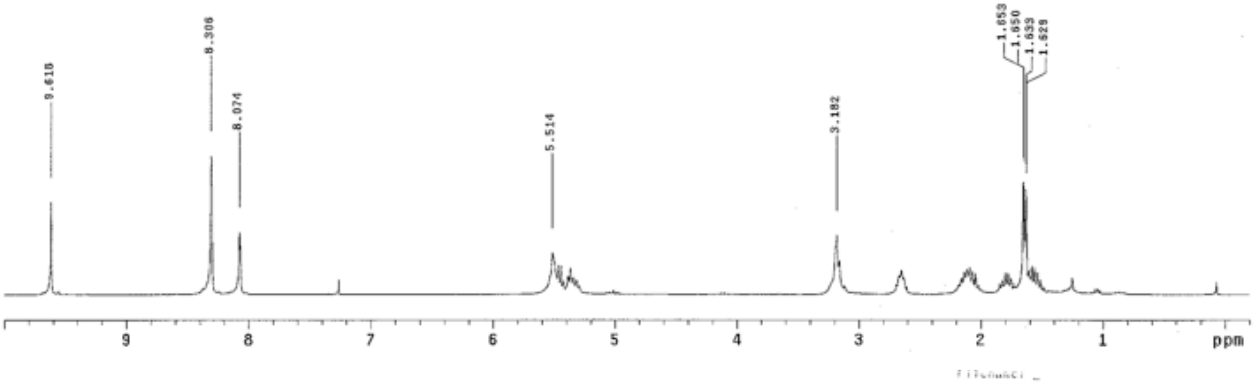
MK-3-225col

Solvent: CDCl3
Ambient temperature
File: MK-3-225col
UNITY-300 "nmr2"

Relax. delay 1.000 sec
Pulse 57.3 degrees
Acq. time 5.000 sec
Width 3761.2 Hz
16 repetitions
OBSERVE H1, 299.9403373 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 36 sec



2.26



MK-3-203-13C

Solvent: CDCl3
Ambient temperature
GEMINI-400BB "nmr8"

Relax. delay 12.880 sec
Pulse 64.8 degrees
Acq. time 0.640 sec
Width 25683.4 Hz
96 repetitions
OBSERVE C13, 100.5868077 MHz
DECOUPLE H1, 400.0288163 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.8 Hz
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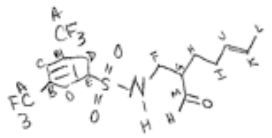

2.26

Chapter 3: Scaffolding Ligands in the Hydroformylation of Secondary 1,1-Disubstituted Allylic Alcohols

I. Project Perspective

While much study has been done involving the hydroformylation of a variety of alkenes to maximize the linear selectivity,[1] stereoselective hydroformylation has been more elusive.[2] One of the first successful ventures in this area came in 1996 from Keiji Yamamoto and coworkers.[2a] In this communication the authors described the examination of a "hydroxyl-directed" diastereoselective hydroformylation. In the course of their research they found that differing protecting groups placed on the hydroxyl group of their 1,1-disubstituted allylic alcohol substrate affects the diastereoselectivity of the reaction (Table 1). The most marked examples of this directing group effect are seen with the acetate (Table 1, Entry 2) and pivolate (Table 1, Entry 3) protecting groups; presumably this selectivity is due to the coordination of the carbonyl oxygen to the rhodium catalyst forming a chelated transition state. For this case, the pivolate group was able to enhance the selectivity of the cyclohexyl substituted substrate to an unprecedented 82:18 anti/syn.

Yamamoto's seminal paper was soon followed by Breit's publication of a corresponding phosphine-based directing group for the syn-selective version of this transformation.[3] A direct comparison of a number of protecting groups can be seen in Table 1, clearly showing the superior syn-selectivity of the *ortho*-

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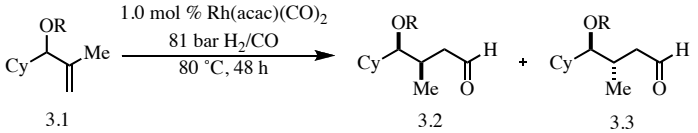
[1] (a) Yu, S.; Chie, Y.; Zhang, X.; Dai, L.; Zhang, X. *Tetrahedron Lett.* **2009,** *50,* 5575-5577. (b) Breit, B.; Seiche, W. *J. Am. Chem. Soc.* **2003,** *125,* 6608-6609. and the references therein.

[2] (a) Doi, T.; Komatsu, H.; Yamamoto, K. *Tetrahedron Lett.* **1996**, *37*, 6877-6880. (b) Breit, B. *Acc. Chem. Res.* **2003,** *36,* 264-275.

[3] Breit, B. *Angew. Chem. Int. Ed.* **1996**, *35,* 2835-2837. A full account of Breit's work in this area can be found in the following review: Breit, B. *Acc. Chem. Res.* **2003,** *36,* 264-275.

diphenylphosphanylbenzoate (*o*-DPPB) group (Table 1, Entry 6). The substrate scope of diastereoselective hydroformylation using *o*-DPPB as a directing group was expanded to include a variety of substitution patterns about the 1,1-disubstituted olefin (Figure 1), and selectivities were enhanced by increasing the sterics of the olefin.

Table 1. Diastereoselective Hydroformylation of *o*-Substituted 1,1-Disubstituted Allylic Alcohols

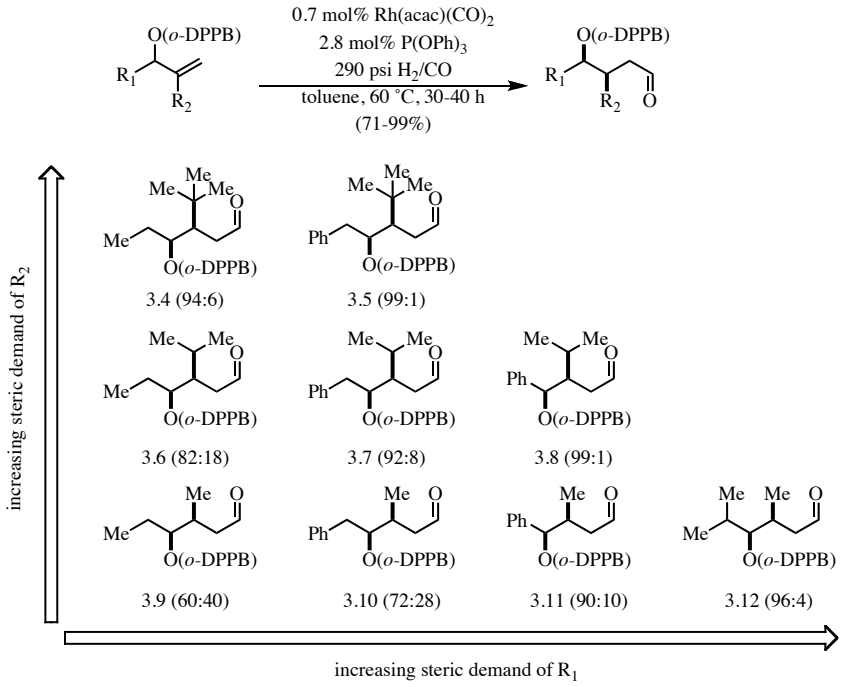


3.1 3.2 syn 3.3 anti

Entry	R	Convn	syn:anti
1	H	96	48:52
2	Ac	84	22:78
3	Piv	89	18:82
4	TBS	91	25:75
5	TBDPS	96	31:69
6*	*o*-DPPB	81	95:5

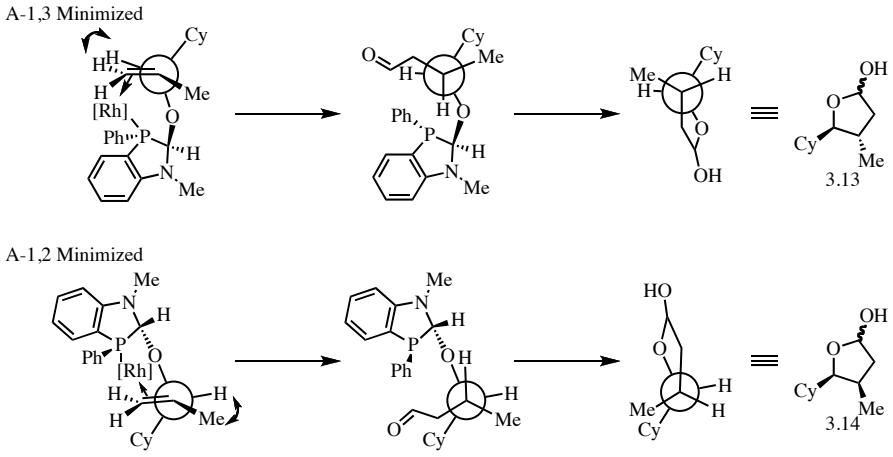
* 0.7 mol % $Rh(acac)(CO)_2$, 2.8 mol % $P(OPh)_3$, 20 bar H_2/CO, 90 ˚C, 24 h

Figure 1. Substrate Scope of *o*-DPPB Directed Hydroformylation



In preliminary studies our group has begun to explore the *catalytic* diastereoselective hydroformylation of geminal olefins. This process forms synthetically useful syn-functionalized lactones.[4] Secondary 1,1-disubstituted allylic alcohols are more difficult substrates for the hydroformylation reaction. Despite this lower reactivity, initial studies yielded 60-80% conversion under relatively mild conditions. Initial results using only a catalytic amount of ligand **I** are promising, producing selectivities that are not far from those of stoichiometric reactions.

Figure 2. Directed Hydroformylation of 1,1-Disubstituted Allylic Alcohols Using Ligand **I**



The directed reaction using scaffolding ligand **I** is hypothesized to go through an A-1,2 minimized pathway[5] to produce the expected syn-substituted lactones (Figure 2, cmpd **3.14**).

II. Initial Studies

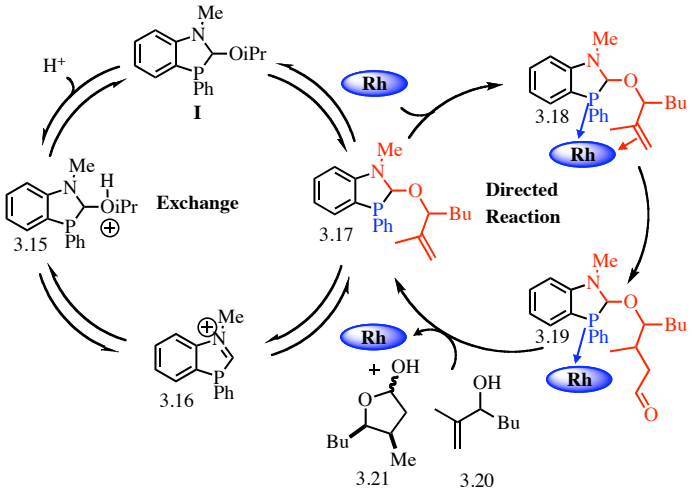
Rapid exchange is a crucial aspect of the successful directing group ability of a scaffolding ligand in any reaction. It was found that exchange of **I** with compound **3.20**

[4] (a) Otsuka, K.; Zenibaya, Y.; Itoh, M. *Agr. Biol. Chem.* **1974**, *38*, 485. (b) Mori, K.; Umemura, T. *Tetrahedron Lett.* **1977**, *33*, 289.

[5] A-1,2 model is similar to that proposed in the Breit review[3]

(Scheme 1) occurs very slowly at room temperature. When heated to 100 ˚C, exchange occurs, and the solution equilibrates over the course of *ca.* 7 days. Adding a small amount (0.0025 equiv) of *para*-toluenesulfonic acid causes the exchange to occur very rapidly.[6] Presumably the acid catalyzes the exchange pathway as shown in Scheme 1. In this process a mixture of diastereomers of ligand is formed; equilibration is complete within 2-3 h to afford a diastereomer ratio of 78:22.

Scheme 1. Proposed Catalytic Cycle for 1,1-Disubstituted Allylic Alcohol Hydroformylation



Once the substrate exchanges onto the ligand, it is important to prove that it indeed directs the reaction towards the predicted product. In order to test this important aspect of our directing group strategy, we pre-exchanged ligand **I** and substrate **3.20** to form compound **3.17** (Scheme 1). This experiment should theoretically constitute a "best case scenario," where all hydroformylation is proceeding through the directed pathway. This stoichiometric reaction yields a selectivity of 70:30 syn/anti. This results suggests that the ligand is moderately directing for the syn product through the intramolecular chelate pathway. The slightly lowered selectivity over the stoichiometric studies done by Breit

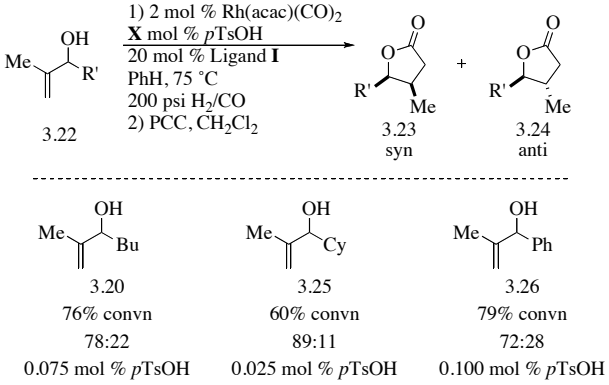
[6] Full exchange typically occurs within 1 h.

(73:27 where Bu is replaced by Et) can mean that either: 1) our scaffolding ligand is not as effective in this transformation or 2) that there is some other pathway that is diminishing the selectivity. If the electronics of the ligand are not ideal for the hydroformylation reaction, the process can have a slower rate and/or the unselective background reaction can become competitive.

III. The Importance of Acid

A series of experiments involving different substitution patterns on the substrate were carried out to better compare our directed pathway with the literature precedent. During the course of these experiments it was discovered that the amount of acid added was important for the conversion as well as the selectivity of the reaction. There appears to be an ideal equivalent of acid for each unique substrate, above and below which there is diminished conversion and/or lower selectivity (Figure 3).

Figure 3: Substrate Scope of Methallylic Alcohols, Acid Effects



These reactions are done with a catalytic amount of ligand that is not pre-exchanged onto substrate, as in the stoichiometric studies done previously. The selectivities are improved and are now comparable to those of the literature precedent.[3] This suggests that there is

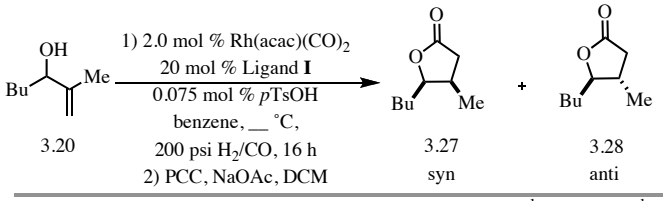
some reason other than ligand affinity for the lower observed selectivity in the stoichiometric reactions. This will be explored further in Section V.

Comparing these substrates, it was decided that optimizations would primarily be done with the substrate (**3.20**, R = Bu) to increase conversion and selectivity. This substrate was chosen because it has the largest range for improvement. Some additional screening would also be focused on **3.25** (R= Cy) to try to increase the conversion.

IV. Optimization of Reaction Conditions

As with all reactions, there are many factors that are available for optimization. In our case, focus was placed on factors such as: ligand and catalyst loading, temperature, reaction gas pressure, solvent, and reaction time. Starting with a simple factor, increasing the temperature of the reaction should increase the conversion of the reaction. In the test case, there is low conversion to desired product at 35-45 ˚C accompanied by high selectivity. As the temperature is increased, the conversion increases and the selectivity remains relatively constant (Table 2).

Table 2. Temperature Screen



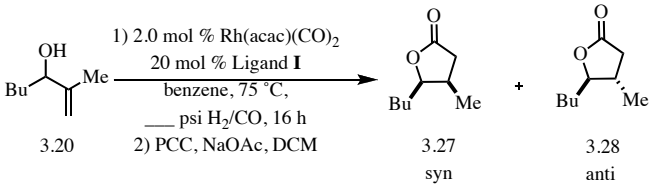
3.20 | 3.27 syn | 3.28 anti

Temperature (˚C)	NMR Convn[a]	Syn[b]	Anti[b]
35	46	N/A	N/A
45	46	82	18
55	53	84	16
65	60	81	19
75	69	83	17
85	68	82	18
95	68	80	20

[a]Determined relative to hexamethylbenzene standard
[b]Determined by GC analysis

As in the case of the allylic sulfonamides (Chapter 2), a syn gas pressure screen was carried out. The increased pressure increases the yield slightly, but does not affect the selectivity dramatically (Table 3). Higher CO pressures are hypothesized to suppress background reaction by inhibiting olefin binding.[7] Increased CO pressure may also facilitate ligand exchange on the metal, which is important in the turnover of the substrate. Therefore this result suggests that there is not a significant problem of background reaction, presumably due to the decreased reactivity of the substrate. In other words, turnover of the substrate occurs more quickly than the hydroformylation reaction.

Table 3. Syn Gas Pressure Screen



3.20 3.27 syn 3.28 anti

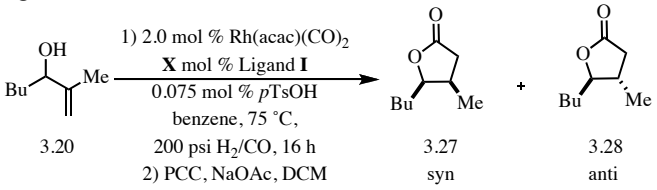
H_2/COPressure (psi)	NMR Convn[a]	Syn[b]	Anti[b]
50	66	81	19
100	62	81	19
200	68	80	20
300	70	79	21
400	71	78	22

[a]Determined relative to hexamethylbenzene standard
[b]Determined by GC analysis

Testing the ligand loading is important because it varies the amount of substrate-bound ligand that is present at a given time. The selectivity is closely tied to the amount of ligand present in the reaction; as the ligand loading is increased from 5 to 10 mol % there is a significant enhancement in selectivity from 61:39 syn/anti to 70:30 (Table 4). This effect levels off between 15 and 20 mol %, where the selectivity and conversion are comparable.

[7] a) van Leeuwen, P. W. N. M; Claver, C. *Rhodium Catalyzed Hydroformylation*. Eds. 1. Kluwer Academic Publishers: Norwell, MA, **2001,** Chapter 4, 63-106. b) van Rooy, A.; Orij, E. N.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics*, **1995,** *14,* 34-43.

Table 4. Ligand Loading Screen



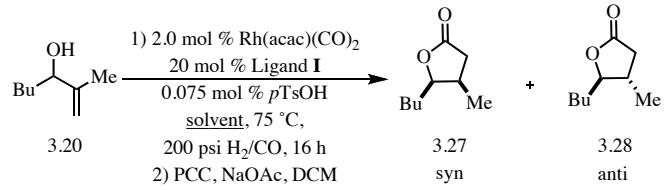
3.20 → 3.27 (syn) + 3.28 (anti)

Mol % **I**	NMR Convn[a]	Syn[b]	Anti[b]
5	63	61	39
10	62	70	30
15	66	77	23
20	66	75	25

[a]Determined relative to hexamethylbenzene standard
[b]Determined by GC analysis

Solvent can play a large role in any reaction.[8] THF, MeCN, and EtOAc all effected lower conversions, potentially due to competitive coordination of the solvent to the catalyst, whereas, toluene is very similar to benzene for these substrates.

Table 5. Solvent Screen



3.20 → 3.27 (syn) + 3.28 (anti)

Solvent	Mol % pTsOH	NMR Convn[a]	Syn[b]	Anti[b]
THF	0	55	50	50
THF	0.1	46	79	21
THF	0.2	48	80	20
MeCN	0	40	69	31
MeCN	0.1	41	64	36
MeCN	0.2	36	62	38
Toluene	0	65	58	42
Toluene	0.1	68	82	18
Toluene	0.2	68	82	18
EtOAc	0	26	57	43
EtOAc	0.1	29	55	45
EtOAc	0.2	29	55	45

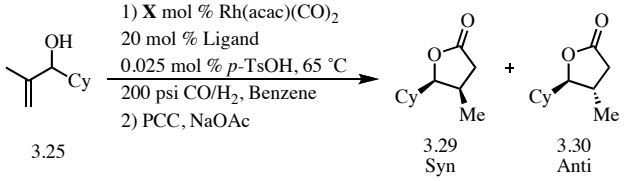
[a]Determined relative to hexamethylbenzene standard
[b]Determined by GC analysis

[8] For a recent review on solvent effects in organic reactions see: Cainelli, G.; Galletti, P.; Giacomini, D. *Chem. Soc. Rev.***2009,** *38,* 990-1001.

Other ways to increase the conversion include: 1) increasing the rhodium catalyst loading, 2) including additives to increase the reactivity of the catalyst, and 3) increasing the time of reaction. It has been found that in all of these cases, an increase in the conversion leads to a decrease in the selectivity.

When the rhodium loading is increased, a slight increase in the conversion is observed, accompanied by a complementary decrease in selectivity (Table 6). This change in selectivity can be attributed to an increase in the background hydroformylation reaction. While the increase in rhodium concentration affects the amount of catalyst-bound ligand, it does not change the amount of substrate-bound ligand formed *in situ*; therefore leading to the same amount of directed reaction. The amount of this increase is small because of the inherent difficulty of these substrates in hydroformylation.

Table 6. Increased Catalyst Loading



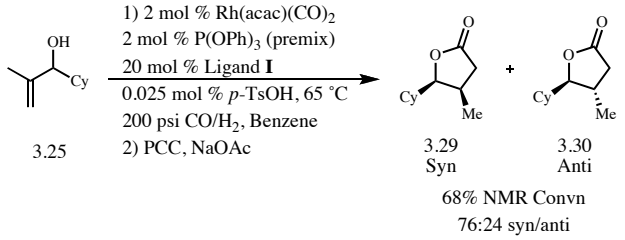
Mol % Rhodium	NMR Convn.[a]	Syn[b]	Anti[b]
2	40	89	11
4	52	85	15
6	57	79	21

[a]Determined relative to hexamethylbenzene standard
[b]Determined by GC analysis

Triphenylphosphite was helpful as an additive to increase the reactivity of rhodium in a study by Breit.[3] In the literature precedent, the phosphite ligand generates a more active catalyst to enhance reactivity. An attempt to apply this strategy towards our

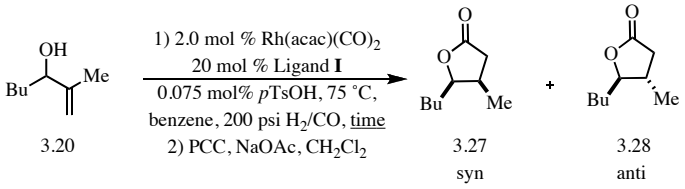
system led only to an increase in the background reaction to yield higher conversion and lower selectivity (Figure 4).

Figure 4. Testing of Hydroformylation Using a Phosphite Additive



Lastly, increasing the reaction time from 16 to 48 h led to a continuation of the emerging trend of increased conversion leading to decreased diastereoselectivity (Table 7). This drop in selectivity can be construed one of two ways: 1) the rate of directed reaction has dropped to a point where the background reaction now outcompetes the directed reaction; or 2) decomposition of scaffolding ligand **I** during the course of the reaction, forms a ligand that is unselective. Considering these options, if the reaction is partitioned into two time blocks, it appears as though the increase in conversion from 16 to 48 h occurs with a selectivity of *ca.* 50:50 ratio.

Table 7. Increased Reaction Time

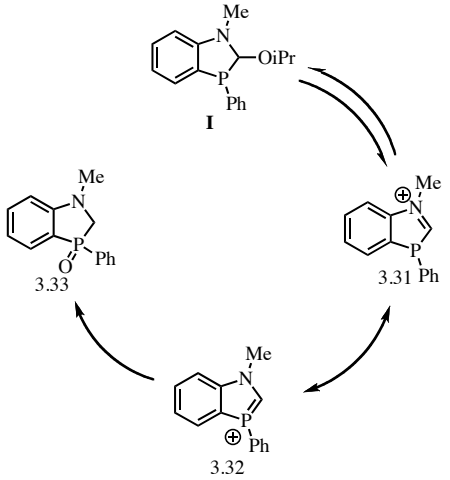


Time (h)	NMR Convn.[a]	Syn[b]	Anti[b]
16	66	83	17
48	77	60	40

[a]Determined relative to hexamethylbenzene standard
[b]Determined by GC analysis

A decomposition product from ligand **I** has been isolated by members of our group from reaction mixtures and independent studies. A crystal structure obtained by Thomas Lightburn has determined its structure to be that of **3.33**. We hypothesize that during the course of the reaction, the decomposition pathway (Scheme 2) competes with hydroformylation; between 16 and 48 h, the ligand is converted to **3.33** and proceeds through a non-directed pathway. To lend credence to this hypothesis, the isolated ligand **3.33** was added to a typical hydroformylation in place of ligand **I** to afford a 57% yield of a 49:51 mixture of syn/anti products. The proposed pathway (Scheme 2) posits that decomposition occurs after iminium **3.31** has formed. The phosphonium ion (Scheme 2, **3.32**) although it is a small contributor in the resonance structure, can be irreversibly quenched through nucleophilic attack of an oxygen substrate (or water). Subsequent protonation of the resulting resulting ylide provides access to oxide **3.33**. It is possible that blocking attack on phosphorous could lead to more stable ligands by slowing this pathway.

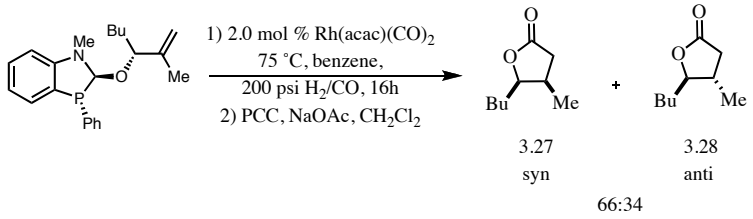
Scheme 2. Proposed Decomposition Pathway



V. Reactions of a Single Diastereomer

When substrate **3.17** and ligand **I** are exchanged in the presence of a catalytic amount of acid, a mixture of diastereotopic ligands is formed. These diastereomers equilibrate completely within 2-3 h to a ratio of 78:22. More information about exchange of ligand **I** and substrate can be found in section II. When the results of stoichiometric hydroformylation of the mixture of diastereomers are compared to the catalytic use of ligand **I,** the reason for a discrepancy in selectivity is unknown. It was first hypothesized that the electronics of the ligand metal binding site were not ideal for the hydroformylation reaction. The enhanced selectivity of the catalytic reaction clearly show that this initial hypothesis is incorrect and that there is some other cause.

Figure 5. Hydroformylation of a Single Diastereomer



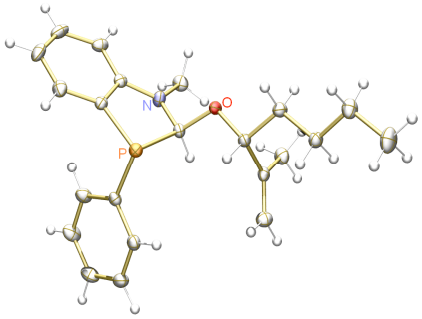
3.27 syn — 3.28 anti

66:34

The major diastereomer of substrate-bound ligand (Figure 6)[9] can be selectively crystallized. Subsequent stoichiometric hydroformylation results in a selectivity of 66:34 syn/anti (Figure 5); whereas a catalytic amount of ligand leads to a selectivity of 83:17. This change in selectivity compels us to believe that a pathway involving the minor diastereomer enhances the selectivity of the catalytic reaction. We hypothesize that synthesizing a conformationally stable chiral ligand will lead to a matched/mismatched pairing that will provide a more selective reaction; even opening the possibility of overturning the syn-selectivity in these substrates.

[9] Phosphorous and substrate stereocenters are R,R in a crystal structure.

Figure 5. Crystal Structure of Substrate Bound Ligand



VI. Conclusions

Initial studies on the hydroformylation of geminally substituted allylic alcohols are promising. Despite their low reactivity when compared with unsubstituted allylic substrates, initial studies yielded 60-80% conversion under relatively mild conditions.[10] Initial results using only a catalytic amount of ligand **I** are promising, producing selectivities that are not far from those of stoichiometric reactions.[11]

Rapid exchange is a crucial aspect of the successful directing group ability of a scaffolding ligand. It has been found that exchange occurs very quickly when utilizing a catalytic amount of *para*-toluenesulfonic acid, yielding a mixture of diastereotopic ligands. The hydroformylation of the resulting mixture gives interesting results, possibly suggesting differing reactivities and/or selectivities of the diastereomers.

A possible solution lies in the synthesis of more stable ligands. If the decomposition pathway (Scheme 2, Section IV) is no longer competitive with the desired reaction, the problem of conversion vs. selectivity would likely be solved.

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[10] A representative procedure is 90 ˚C for 24 h.
[11] Breit, B. *Acc. Chem. Res.* **2003**, *36*, 264-275.

V. Experimental

General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Lithium reagents were titrated against 2-pentanol or 2,6-Di-*tert*-butyl-4-methylphenol (BHT) using 1,10-phenanthroline as the indicator. Flash column chromatography was performed using EMD Silica Gel 60 (230-400 mesh) and ACS grade solvents as received from Fisher Scientific. All experiments were performed in oven or flame dried glassware under an atmosphere of nitrogen or argon using standard syringe and cannula techniques, except where otherwise noted. All reactions were run with dry, degassed solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). ^{1}H, ^{13}C and ^{31}P NMR were performed on either a Varian Gemini-2000 400 MHz or a Varian Unity 300 MHz instrument. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. C_6D_6 was degassed by three successive freeze-pump-thaw cycles and stored over 3Å molecular sieves in a dry box under a nitrogen atmosphere. All NMR chemical shifts are reported in ppm relative to residual solvent for ^{1}H and ^{13}C and external standard (neat H_3PO_4) for ^{31}P NMR. Coupling constants are reported in Hz. All IR spectra were gathered on a Bruker Alpha FT-IR equipped with a single crystal diamond ATR module and values are reported in cm^{-1}. All GC analyses were performed on an Agilent Technologies 7890A GC System. High resolution mass spectrometry was performed at the Mass Spectrometry Facility at Boston College by either Mr. Marek Domin or Moriah Gagnon (on a Micromass LCT ESI-MS (positive mode) or a DART). X-ray crystal structure data were

generated in Boston College facilities by Mr. Bo Li. Hydroformylation was performed in an Argonaut Technologies Endeavor® Catalyst Screening System using 1:1 H_2/CO supplied by Airgas, Inc.

Substrate Syntheses and Characterization

The following compounds were made according to literature procedures and matched reported spectra: 2-Isopropoxy-2,3-dihydro-1*H*-benzo[*d*][1,3]azaphosphole **(I)**.[12]

Cmpd 3.20: 2-methylhept-1-en-3-ol[13] To a flame dried 25 mL round bottom flask fitted with reflux condenser was added crushed magnesium turnings (1.01 g) followed by gentle warming under vacuum. After the flask cooled to ambient temperature it was placed under N_2 atmosphere and THF (41 mL) was added. The solution was cooled to 0 ˚C and 2-bromopropene (5.0 g, 3.6 mL) was added slowly to yield a gray cloudy solution that was refluxed at 55 ˚C for 2.5 h. The resulting grignard solution was clear dark green with a small amount of magnesium leftover. This solution was titrated using 2-pentanol and phenanthroline in THF at 25 ˚C to give 0.83 M. The grignard was taken up in a syringe and added dropwise (2 drops/sec) to a 0 ˚C solution of valeraldehyde (2.95 g, 3.65 mL) in THF (24 mL) in a flame dried 250 mL flask. The solution was allowed to warm to ambient temperature overnight after which it was diluted with 75 mL Et_2O and

[12] Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130,* 9210-9211.
[13] (a) Briot, A.; Baehr, C.; Brouillard, A.W.; Mioskowski, C. *J. Org. Chem.* **2004,** *69,* 1374-1377.; (b) Basseti, M.; D'Annibale, A.; Fanfoni, A.; Minissi, F. *Org. Lett.* **2005,** *7*, 1805-1808.

quenched with saturated aqueous NH_4Cl (125 mL). The Et_2O layer was washed with water (2 x 100 mL). The combined water layers were washed with Et_2O (2 x 50 mL). The organic layers were combined and dried over $MgSO_4$, filtered and concentrated to yield a yellow oil. Chromatography (5% EtOAc/Hex) yielded a clear oil that was distilled (105-115 ˚C @ 15 mm Hg) to yield a clear oil (2.7 g, 62%). Spectra matched literature values. **GC Method A:** 2.29 min.

Cmpd 3.25: 1-cyclohexyl-2-methylprop-2-en-1-ol[2]

The procedure for 2-methylhept-1-en-3-ol was followed, substituting cylcohexylcarboxaldehyde for valeraldehyde. Chromatography (5% EtOAc/Hex) afforded an oil that was distilled (120-125 ˚C @ 15 mm Hg) to yield a clear oil (3.62 g, 71%). Spectra matched literature values. **GC Method B:** 4.99 min.

Cmpd 3.26: 2-methyl-1-phenylprop-2-en-1-ol[14]

The procedure for 2-methylhept-1-en-3-ol was followed, substituting benzaldehyde for valeraldehyde. Chromatography (5% EtOAc/Hex) afforded a yellow oil (1.55 g, 80%). Spectra matched literature values. **GC Method B:** 5.62 min.

[14] (a) Miura, K.; Wang, D.; Hosomi, A. *J. Am. Chem. Soc.* **2005**, *127*, 9366-9367.; (b) Reich, H. J.; Shah, S. K.; Chow, F. *J. Am. Chem. Soc.* **1979**, *101*, 6648-6656.

GC Analysis Methods

GC Method A. An Agilent Technologies 7890A GC System equipped with a 7683B Series Injector was used to introduce samples into a J&W Scientific column (HP-5, 30 m, 0.320 mm ID, 0.25 μm film). The GC was run at 110 ˚C for 2 minutes, then the temperature was ramped at 1 ˚C/min. to a final temperature of 125 ˚C. Detection was by FID and data was worked up with Agilent Technologies GC ChemStation software (Rev.B.03.01-SR1). Retention times are reported in minutes.

GC Method B. Identical to GC Method A. After the method reached 125 ˚C, the temperature was maintained for 5 min and then the temperature was ramped at 10 ˚C/min to a final temperature of 200 ˚C. The temperature was maintained for an additional 5 minutes.

Exchange Reactions with Allylic Alcohols

General Exchange Reaction Procedure. The alcohol (38.4 mg, 0.3 mmol) was mixed with ligand **I** (17.1 mg, 0.06 mmol) and *p*-toluenesulfonic acid (428 μL, 5.25×10^{-4} M, 2.25×10^{-4} mmol) in benzene (2.0 mL) and monitored at room temperature in an inert atmosphere sealed NMR tube. The reaction progress was followed by ^{31}P NMR. Ligand **3.17:** ^{31}P NMR: –19.8 ppm and –26.1 ppm.

Exchange Reaction Procedure Without Added Acid. The alcohol (38.4 mg, 0.3 mmol) was mixed with ligand **I** (17.1 mg, 0.06 mmol) in benzene (2.0 mL) and heated to 100 ˚C in an inert atmosphere sealed NMR tube. The reaction progress was followed by ^{31}P NMR. Ligand **3.17:** ^{31}P NMR: –19.8 ppm and –26.1 ppm.

Optimization of Branched Selective Hydroformylation

General Hydroformylation Procedure. The Endeavor was charged with 500 uL of benzene per reaction well to fill the void volume between reactor wall and reaction tube, and oven dried glass reaction vials were placed in the Endeavor. The Endeavor was sealed and purged with nitrogen (4x100 psi). The necessary injection(s) were made (see below). The Endeavor was purged with nitrogen (1x100 psi), stirring was started at 250 rpm, and the Endeavor was heated to 65 ˚C and held for 10 minutes. Stirring was stopped, the Endeavor was charged with H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at constant temperature of 65 ˚C and pressure of H_2/CO for 16 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction vials were removed from the Endeavor, a solution of hexamethylbenzene (200 μL, 0.1 M) was added, and the sample was concentrated. ^{1}H NMRs were taken to determine conversion. The crude residue was dissolved in CH_2Cl_2 and pyridinium chlorochromate (3 equiv.), sodium acetate (0.5 equiv.), and 3Å molecular sieves were added and the solution was agitated on an orbital shaker for 12 hours. The reaction was eluted through a plug of silica gel (50% EtOAc/Hex). GC analysis of the solutions were used to determine diastereoselectivities. The sample was compared to

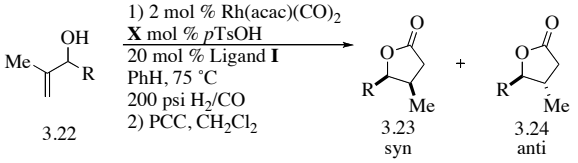
hexamethylbenzene (retention time: 13.52 min) as an internal standard.

General Optimization Procedure. The General Hydroformylation procedure was followed. A solution of 2-methylhept-1-en-3-ol (38.4 mg, 0.30 mmol), ligand **I** (20 mol %, 17.1 mg, 0.06 mmol), *p*-toluenesulfonic acid (433 μL, 5.25×10^{-4} M, 2.25×10^{-4} mmol), and dicarbonylacetylacetonato rhodium (I) (2.0 mol %, 1.3 mg, 0.006 mmol) in benzene (1.50 mL) was prepared in a dry box and injected into the Endeavor via syringe. An additional 500 μL of benzene was added to wash the injection port. The Endeavor was kept at a constant temperature of 65 ˚C and a H_2/CO pressure of 200 psi.

General 3.25 Optimization Procedure. The General Hydroformylation procedure was followed. A solution of 1-cyclohexyl-2-methylprop-2-en-1-ol (46.2 mg, 0.30 mmol), ligand **I** (20 mol %, 17.1 mg, 0.06 mmol), *p*-toluenesulfonic acid (143 μL, 5.25×10^{-4} M, 7.5×10^{-5} mmol), and dicarbonylacetylacetonato rhodium (I) (2.0 mol %, 1.3 mg, 0.006 mmol) in benzene (1.50 mL) was prepared in a dry box and injected into the Endeavor via syringe. An additional 500 μL of benzene was added to wash the injection port. The Endeavor was kept at a constant temperature of 65 ˚C and a H_2/CO pressure of 200 psi.

Figure 3 (% Acid Screen): The General Optimization Procedure was followed, except a varying amount of acid solution was added.

Full table of results for % acid screen:



R	Mol % *p*TsOH	NMR Convn[a]	Syn[b]	Anti[b]
Bu	0	73	61	39
Bu	0.05	71	78	22
Bu	0.10	66	81	19
Bu	0.20	72	82	18
Cy	0	51	75	25
Cy	0.05	54	89	11
Cy	0.10	55	89	11
Cy	0.20	35	82	18
Ph	0	63	53	47
Ph	0.05	79	70	30
Ph	0.10	66	72	28
Ph	0.20	61	72	28

[a]Determined relative to hexamethylbenzene standard
[b]Determined by GC analysis

Table 2 (Temperature Screen): The General Optimization Procedure was followed, except the temperature was varied.

Table 3 (Pressure Screen): The General Optimization Procedure was followed, except the temperature was kept at a constant 75 ˚C and the pressure of H_2/CO was varied.

Table 4 (Ligand Loading Screen): The General Optimization Procedure was followed, except the mol % of ligand **I** was varied and the temperature was kept at a constant 75 ˚C.

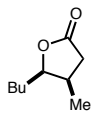
Table 5 (Solvent Screen): The General Optimization Procedure was followed, except the solvent and mol % *p*-toluenesulfonic acid was varied.

Table 6 (Increased Catalyst Loading Screen): The General 3.25 Optimization Procedure was used and the mol % of dicarbonylacetylacetonato rhodium (I) was varied.

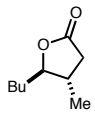
Figure 4 (Phosphite Additive Test): The General 3.25 Optimization Procedure was used, triphenylphosphite (2.0 mol %, 18.6 mg, 0.006 mmol) was added to the reaction mixture.

Table 7 (Increased Reaction Time): The General Optimization Procedure was followed, except the reaction was allowed to proceed for 48 h.

Product Characterization



Cmpd 3.27: (syn)-5-butyl-4-methyldihydrofuran-2(3*H*)-one.[15] The General Optimization Procedure was used. Chromatography (1-5% EtOAc/Hex). Spectra matched literature values. **GC Method A**: 7.11 min.



Cmpd 3.28: (anti)-5-butyl-4-methyldihydrofuran-2(3*H*)-one.[16] The General Optimization Procedure was used. Chromatography (1-5% EtOAc/Hex). Spectra matched literature values. **GC Method A**: 8.15 min.

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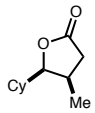
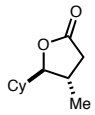
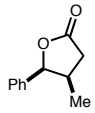
[15] Ozeki, M.; Hashimoto, D.; Nishide, K.; Kajimoto, T.; Node, M. *Tetrahedron: Asymmetry.* **2005**, *16*, 1663-1671.



Cmpd 3.29: (syn)-5-cyclohexyl-4-methyldihydrofuran-2(3*H*)-one.[4] The General 3.25 Optimization Procedure was used. Chromatography (1-5% EtOAc/Hex). Spectra matched literature values. **GC Method B**: 21.43 min.



Cmpd 3.30: (anti)-5-cyclohexyl-4-methyldihydrofuran-2(3*H*)-one.[17] The General 3.25 Optimization Procedure was used. Chromatography (1-5% EtOAc/Hex). Spectra matched literature values. **GC Method B**: 19.98 min;**^{13}C NMR** ($CDCl_3$, 100 MHz) δ 176.9, 91.7, 41.6, 37.4, 32.4, 29.2, 28.0, 26.4, 26.2, 25.9, 19.5.



Cmpd 3.31: (syn)-4-methyl-5-phenyldihydrofuran-2(3*H*)-one.[4,5b] The General Hydroformylation procedure was followed. A solution of 2-methylhept-1-en-3-ol (44.4 mg, 0.30 mmol), ligand **I** (20 mol %, 17.1 mg, 0.06 mmol), *p*-toluenesulfonic acid (0.05 mol %, 300μL, $5x10^{-4}$ M, $1.5x10^{-4}$ mmol), and dicarbonylacetylacetonato rhodium (I) (2.0 mol %, 1.3 mg, 0.006 mmol) in benzene (1.50 mL) was prepared in a dry box and injected into the Endeavor via syringe. An additional 500 μL of benzene was added to

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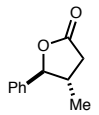
[16] (a) Ghosh, M.; Bose, S.; Ghosh, S. *Tetrahedron Lett.* **2008**, *49*, 5424-5426.; (b) Fang, J.; Hong, B.; Liao, L. *J. Org. Chem.* **1987**, *52*, 855-861.
[17] Frenette, R.; Monette, M.; Bernstein, M. A.; Young, R. N.; Verhoeven, T. R. *J. Org. Chem.* **1991**, *56*, 3083-3089.

wash the injection port. The Endeavor was kept at a constant temperature of 65 ˚C and a H_2/CO pressure of 200 psi. Chromatography (1-5% EtOAc/Hex). Spectra matched literature values. **GC Method B**: 19.40 min.



Cmpd 3.32: (anti)-4-methyl-5-phenyldihydrofuran-2(3*H*)-one.[5b,18] The same procedure as (syn)-4-methyl-5-phenyldihydrofuran-2(3*H*)-one was used. Spectra matched literature values. **GC Method B**: 20.03 min.

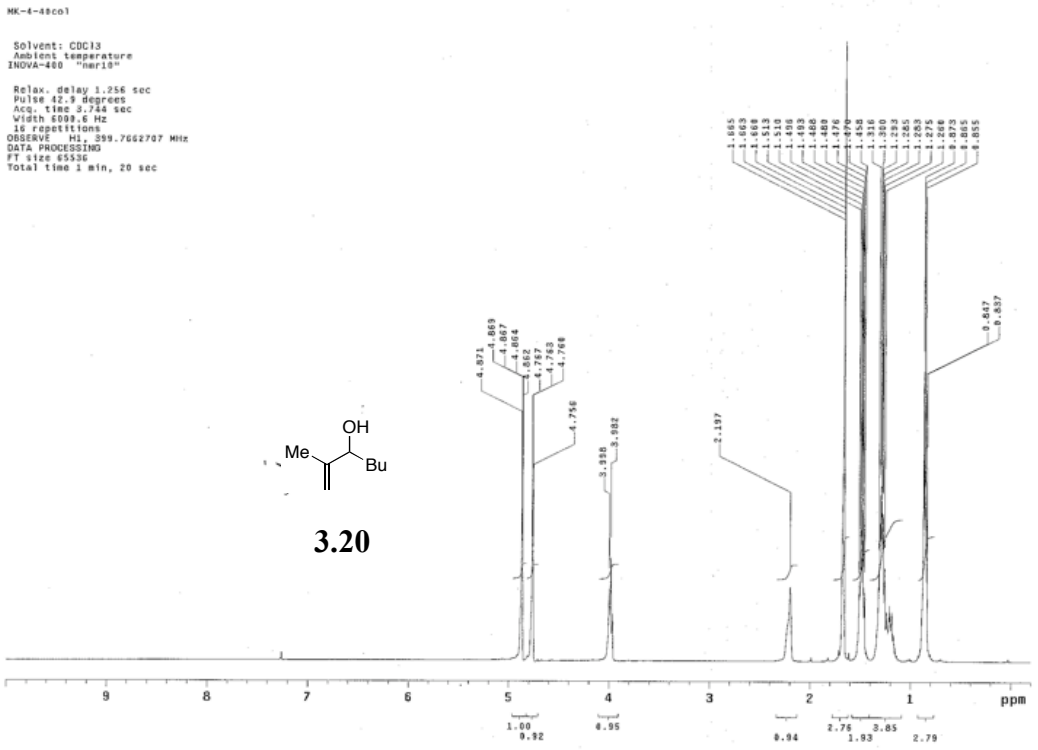
Isolation and Reaction of a Single Diastereomer of Ligand

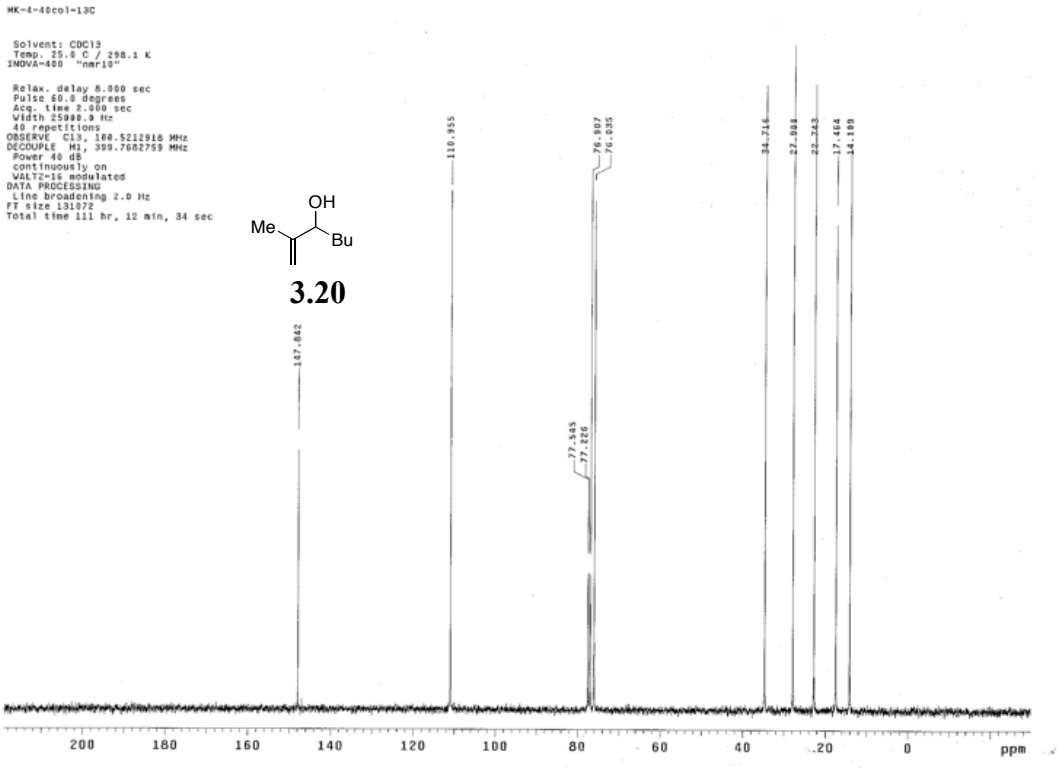
Procedure for Crystallization of 3.34: General Exchange Procedure (above) was followed and the solution of C_6D_6 was concentrated to yield the mixture of diastereomeric ligands as a white solid (100 mg, 100% recovery). The oil was dissolved in pentanes (4.4 mL), filtered, and allowed to cool slowly to –35 ˚C overnight. The resulting crystals were isolated by filtration and washed with cold pentanes.
^{31}P NMR: –26.1 ppm.

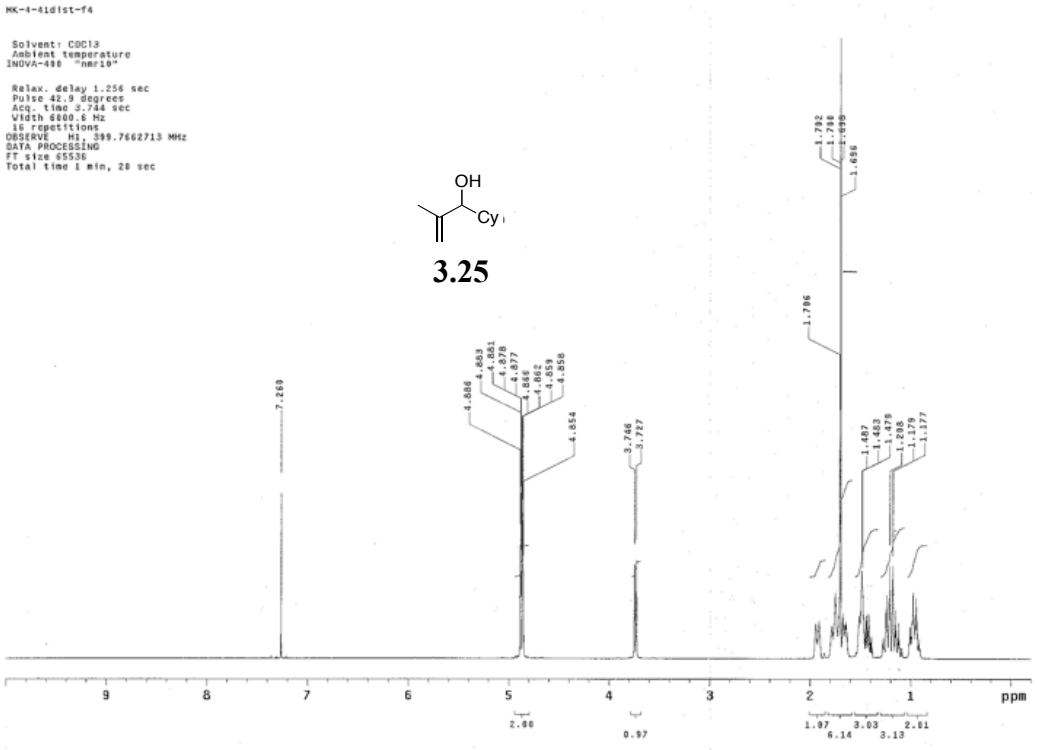
Procedure for Hydroformylation of 3.34: The General Hydroformylation Procedure (above) was followed, except that the temperature was kept at a constant of 75 ˚C. A solution of ligand **3.34** (21.2 mg, 0.06 mmol) and dicarbonylacetylacetonato rhodium (I) (10.0 mol %, 1.3 mg, 0.006 mmol) in benzene (1.50 mL) was prepared in a dry box and

[18] Ressig, H.; Angert, H. *J. Org. Chem.* **1993**, *58*, 6280-6285.

injected into the Endeavor via syringe. An additional 500 μL of benzene was added to wash the injection port. The Endeavor was kept at a constant H_2/CO pressure of 200 psi.


MK-4-48col
Solvent: CDCl3
Ambient temperature
INOVA-400 "nmr10"
Relax. delay 1.256 sec
Pulse 42.9 degrees
Acq. time 3.744 sec
Width 6000.6 Hz
16 repetitions
OBSERVE H1, 399.7662707 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 20 sec
OH
Me
Bu
3.20
ppm


MK-4-48col-13C
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "nmr10"
Relax. delay 5.000 sec
Pulse 60.0 degrees
Acq. time 2.000 sec
Width 25000.0 Hz
40 repetitions
OBSERVE C13, 100.5212918 MHz
DECOUPLE H1, 399.7682759 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 111 hr, 12 min, 34 sec
OH
Me
Bu
3.20
ppm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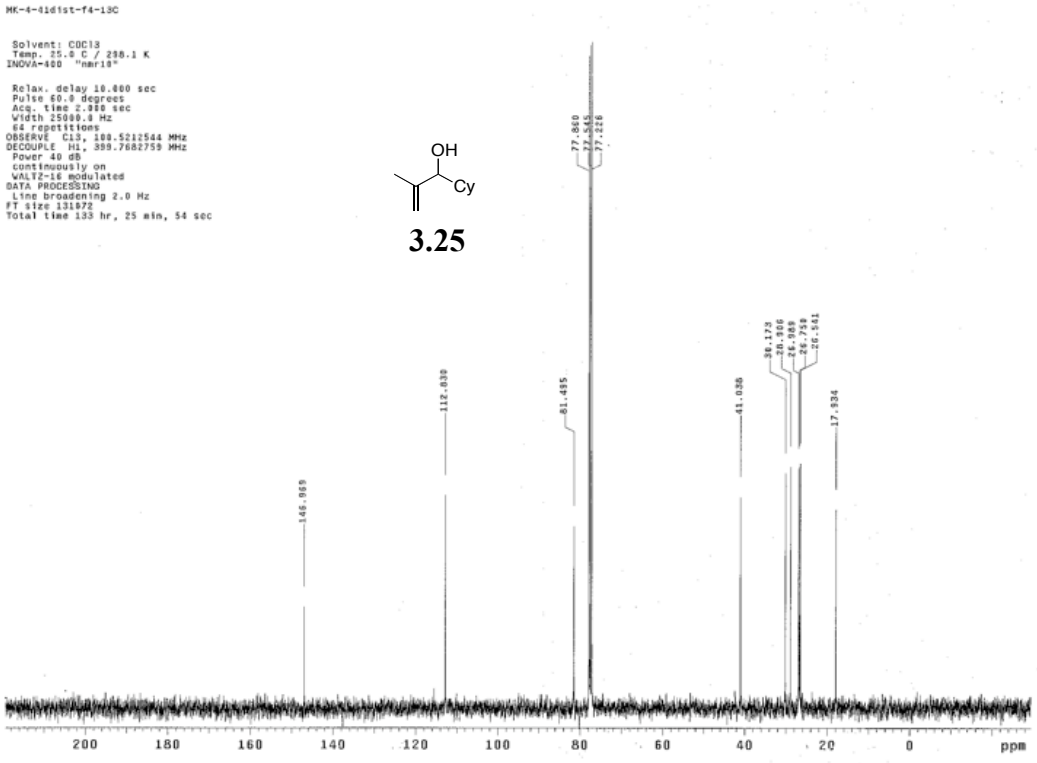
Solvent: CDCl3
Ambient temperature
INOVA-400 "nmr10"
Relax. delay 1.256 sec
Pulse 42.9 degrees
Acq. time 3.744 sec
Width 6000.6 Hz
16 repetitions
OBSERVE H1, 399.7662713 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 28 sec
OH
Cy
3.25
7.269
4.888
4.883
4.881
4.878
4.877
4.866
4.862
4.859
4.856
4.854
3.746
3.727
1.792
1.788
1.686
1.706
1.487
1.483
1.478
1.208
1.179
1.177
9
8
7
6
5
4
3
2
1
ppm
2.00
0.97
1.07
3.03
2.01
6.14
3.13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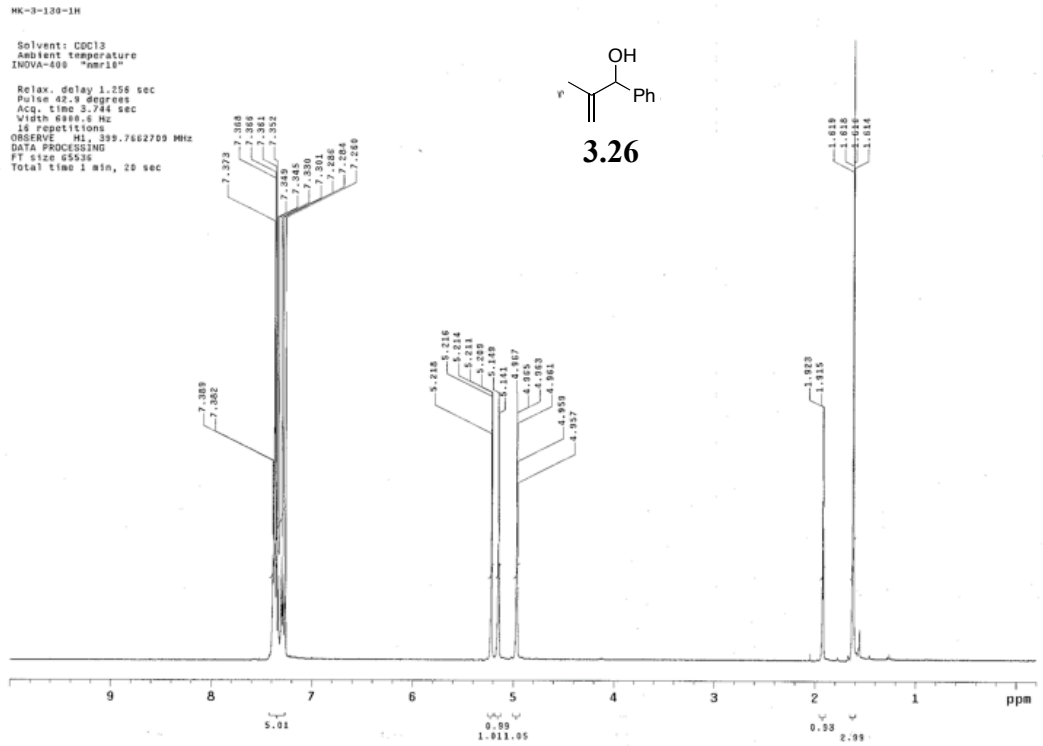
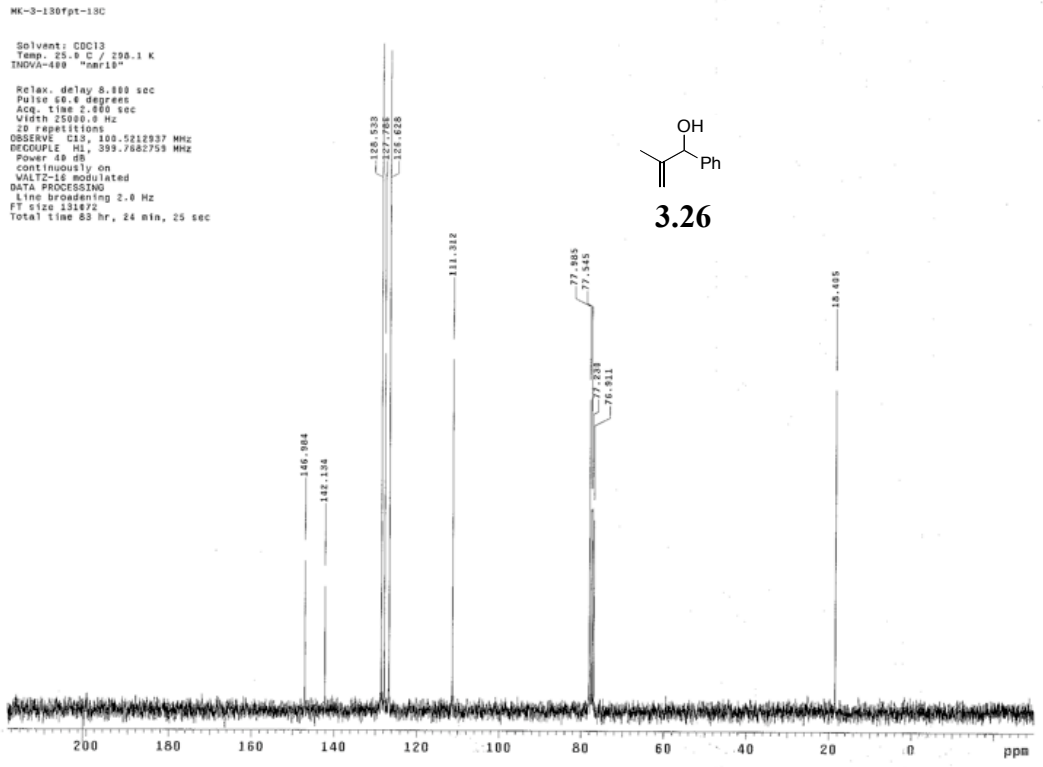
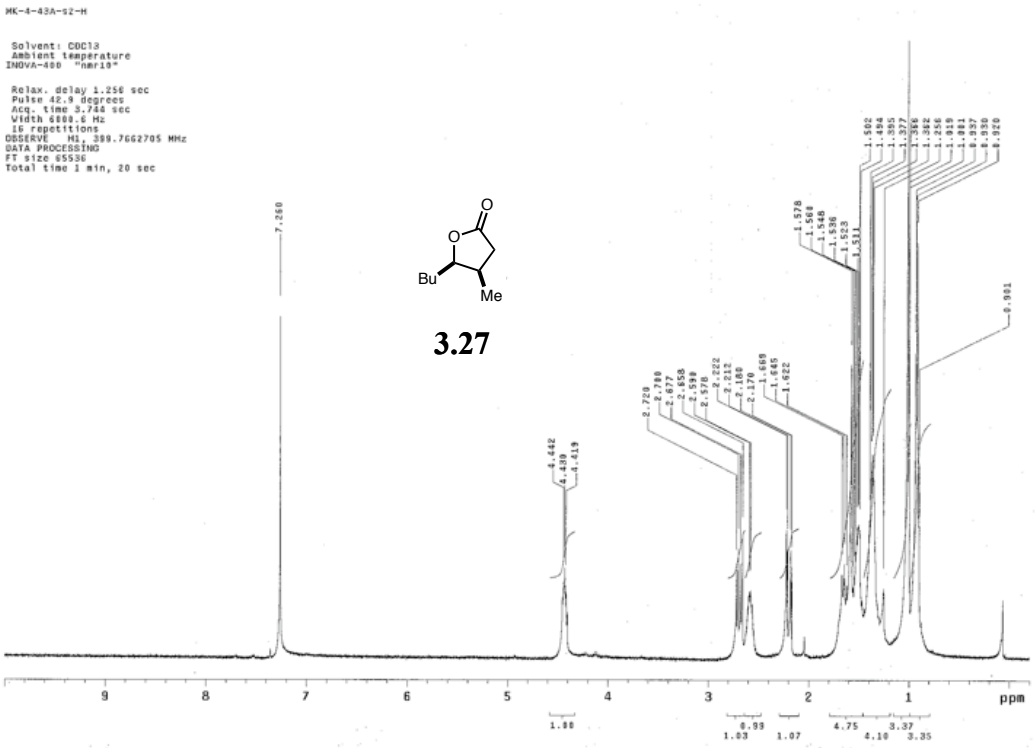
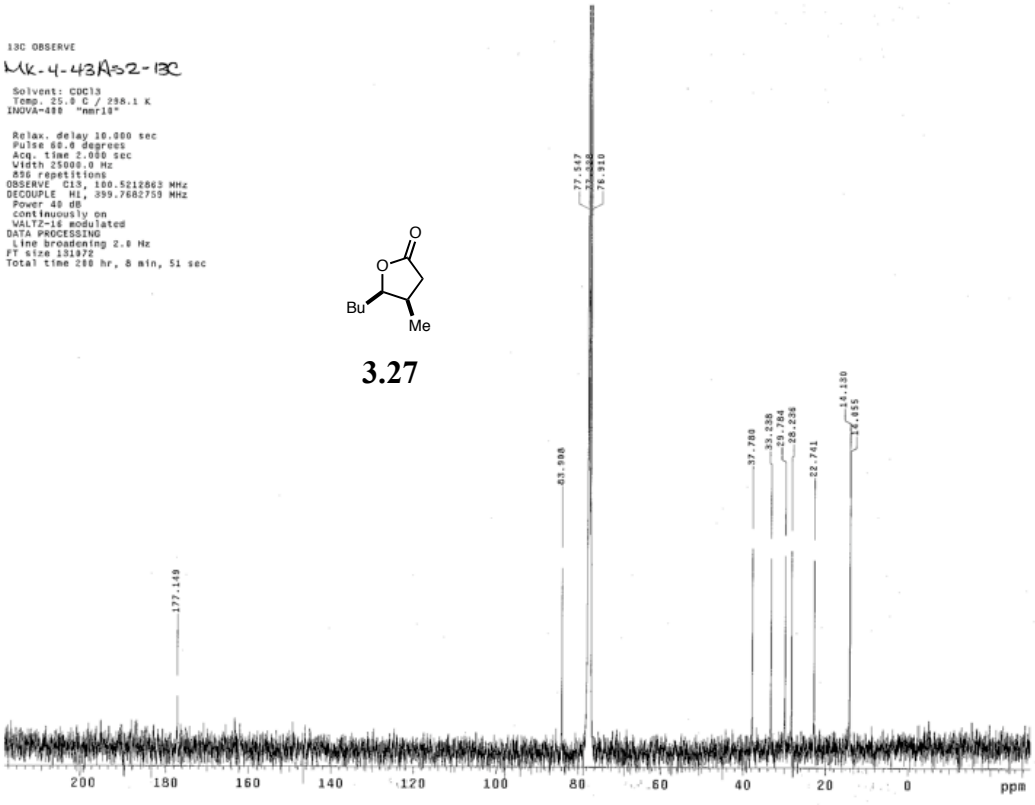
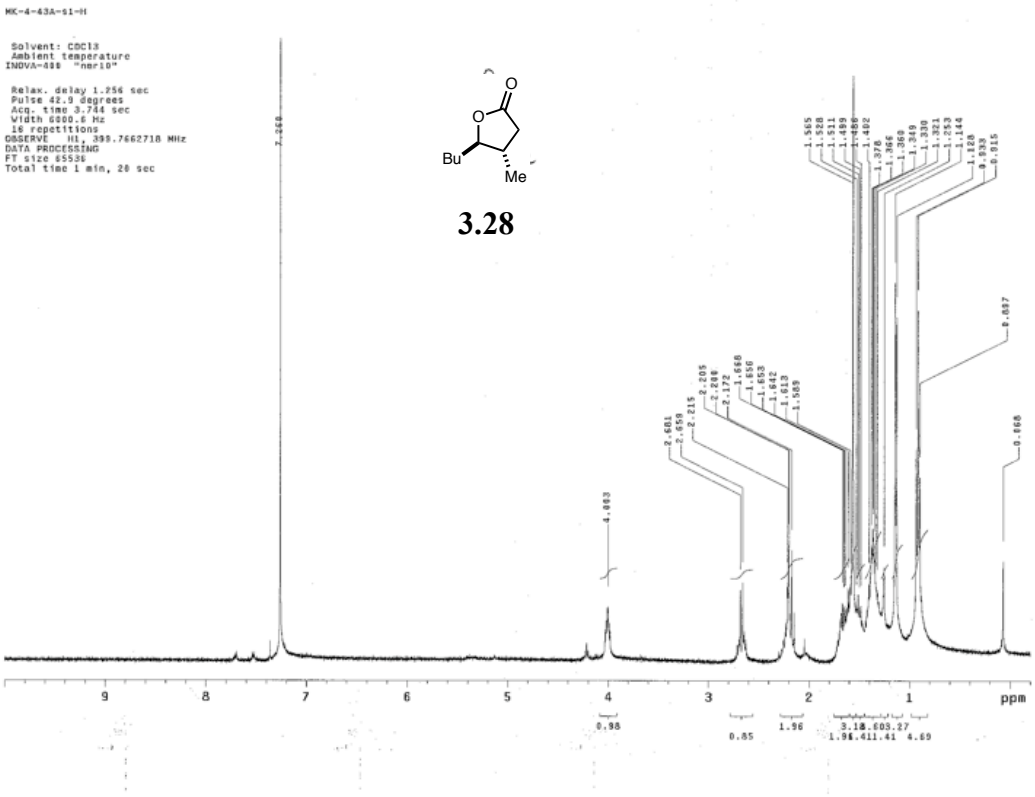
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "nmr18"
Relax. delay 10.000 sec
Pulse 60.0 degrees
Acq. time 2.000 sec
Width 25000.0 Hz
64 repetitions
OBSERVE C13, 100.5212544 MHz
DECOUPLE H1, 399.7682759 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 133 hr, 25 min, 54 sec
OH
Cy
3.25
77.060
77.444
77.226
146.969
112.039
81.495
41.036
30.173
28.806
26.989
26.759
26.561
17.934
200
180
160
140
120
100
80
60
40
20
0
ppm


MK-3-130-1H
Solvent: CDCl3
Ambient temperature
INOVA-400 "nmr10"
Relax. delay 1.256 sec
Pulse 42.9 degrees
Acq. time 3.744 sec
Width 6988.6 Hz
16 repetitions
OBSERVE H1, 399.7662709 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 20 sec
OH
Ph
3.26
ppm

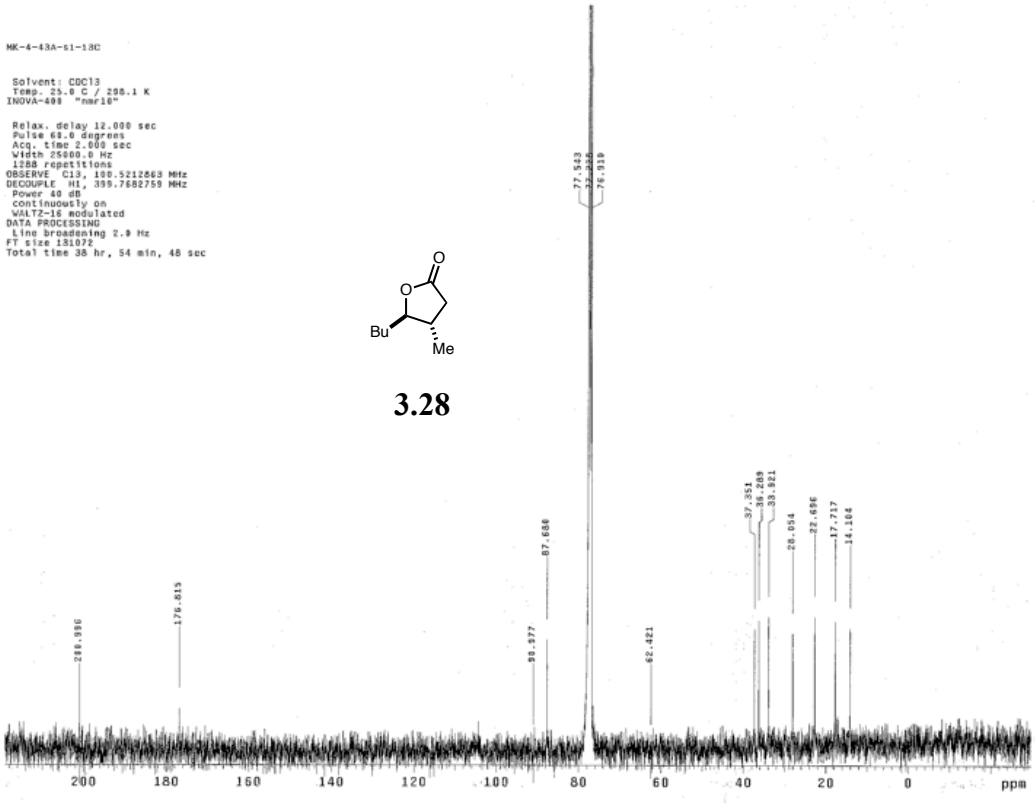

MK-3-130fpt-13C
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "nmr10"
Relax. delay 8.880 sec
Pulse 60.0 degrees
Acq. time 2.660 sec
Width 25000.0 Hz
20 repetitions
OBSERVE C13, 100.5212937 MHz
DECOUPLE H1, 399.7682759 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 83 hr, 24 min, 25 sec
OH
Ph
3.26
ppm


MK-4-43A-S2-H
Solvent: CDCl3
Ambient temperature
INOVA-400 "nmr19"
Relax. delay 1.256 sec
Pulse 42.9 degrees
Acq. time 3.748 sec
Width 6808.6 Hz
16 repetitions
OBSERVE H1, 399.7662705 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 20 sec
7.260
4.442
4.430
4.419
2.729
2.780
2.677
2.658
2.599
2.578
2.222
2.212
2.188
2.170
1.669
1.645
1.622
1.578
1.560
1.548
1.536
1.523
1.511
1.502
1.494
1.395
1.377
1.366
1.352
1.336
1.319
1.081
0.937
0.930
0.920
0.901
Bu
Me
3.27
9
8
7
6
5
4
3
2
1
ppm
1.88
0.99
1.03
1.07
4.75
4.10
3.37
3.35

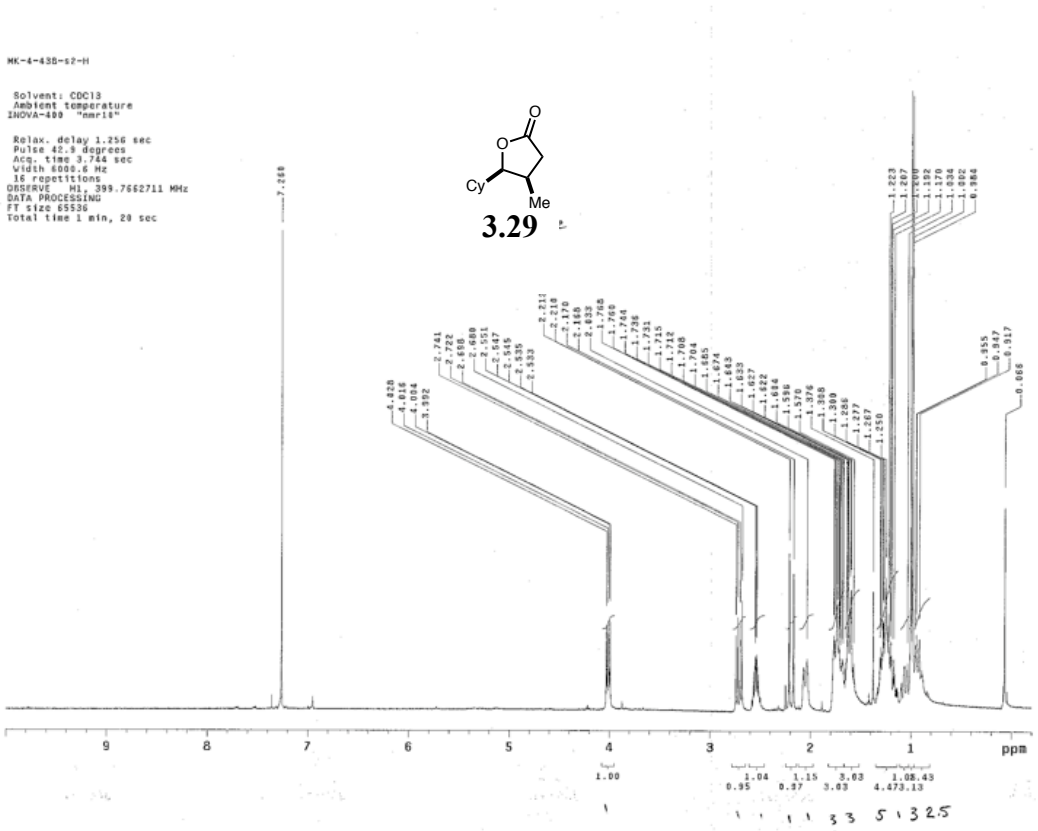

13C OBSERVE
MK-4-43AS2-13C
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "nmr14"
Relax. delay 10.000 sec
Pulse 60.0 degrees
Acq. time 2.000 sec
Width 25000.0 Hz
856 repetitions
OBSERVE C13, 100.5212863 MHz
DECOUPLE H1, 399.7682759 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 280 hr, 8 min, 51 sec
177.149
77.517
77.200
76.910
83.908
37.780
33.238
29.784
26.236
22.741
14.130
13.655
Bu
Me
3.27
200
180
160
140
120
100
80
60
40
20
0
ppm

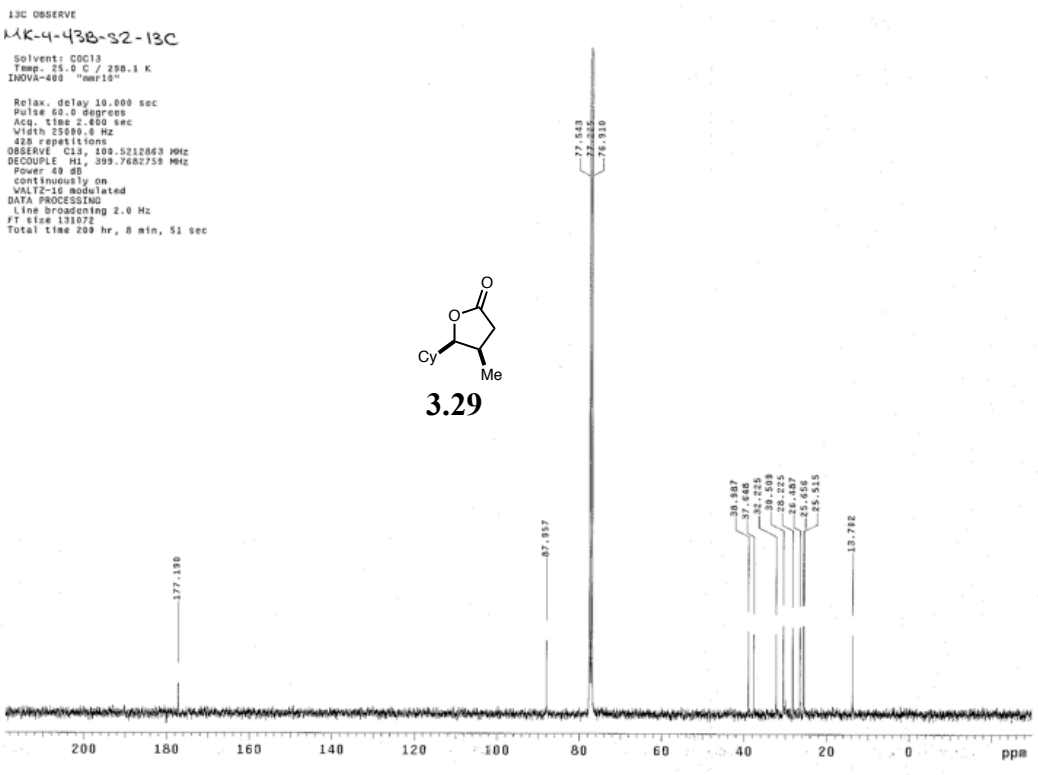

MK-4-43A-s1-H
Solvent: CDCl3
Ambient temperature
INOVA-400 "nmr10"
Relax. delay 1.256 sec
Pulse 42.9 degrees
Acq. time 3.744 sec
Width 6000.6 Hz
16 repetitions
OBSERVE H1, 399.7662718 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 20 sec
Bu
Me
ppm

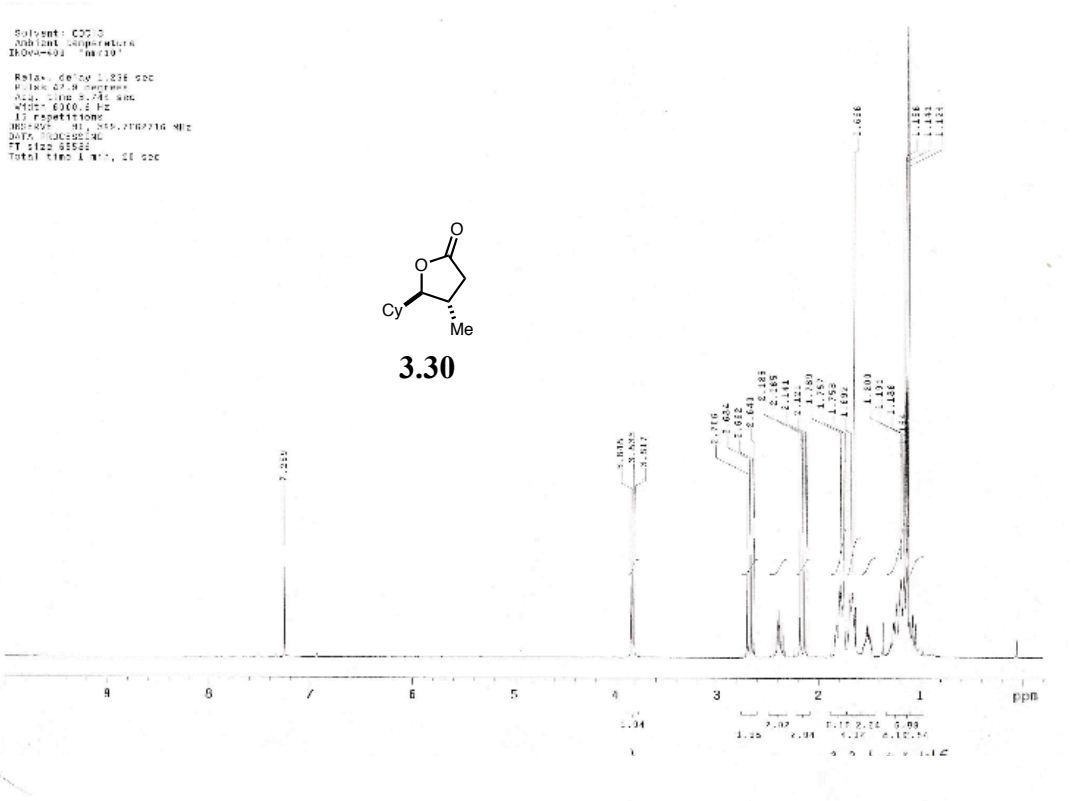
3.28


MK-4-43A-s1-13C
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "nmr10"
Relax. delay 12.000 sec
Pulse 68.0 degrees
Acq. time 2.000 sec
Width 25000.0 Hz
1288 repetitions
OBSERVE C13, 100.5212863 MHz
DECOUPLE H1, 399.7682759 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 38 hr, 54 min, 48 sec
Bu
Me
ppm

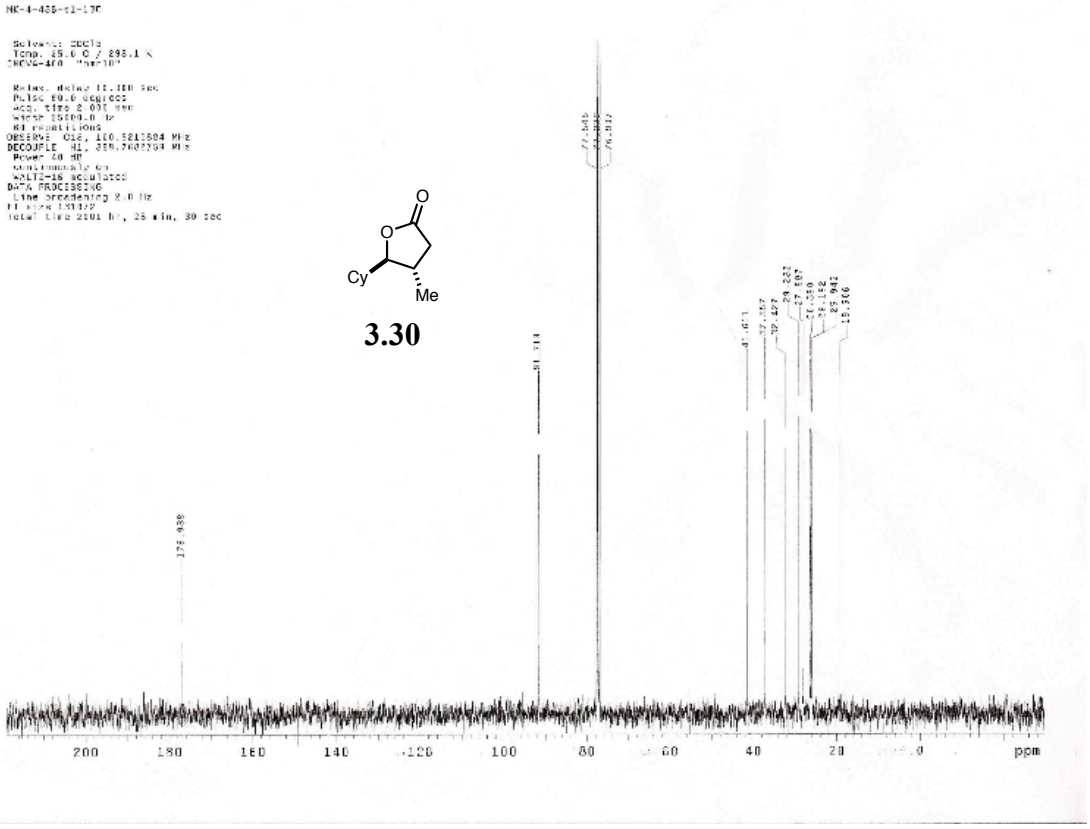
3.28


MK-4-43B-s2-H
Solvent: CDCl3
Ambient temperature
INOVA-400 "nmr18"
Relax. delay 1.256 sec
Pulse 42.9 degrees
Acq. time 3.744 sec
Width 6000.6 Hz
16 repetitions
OBSERVE H1, 399.7662711 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 20 sec
Cy
Me
3.29
ppm

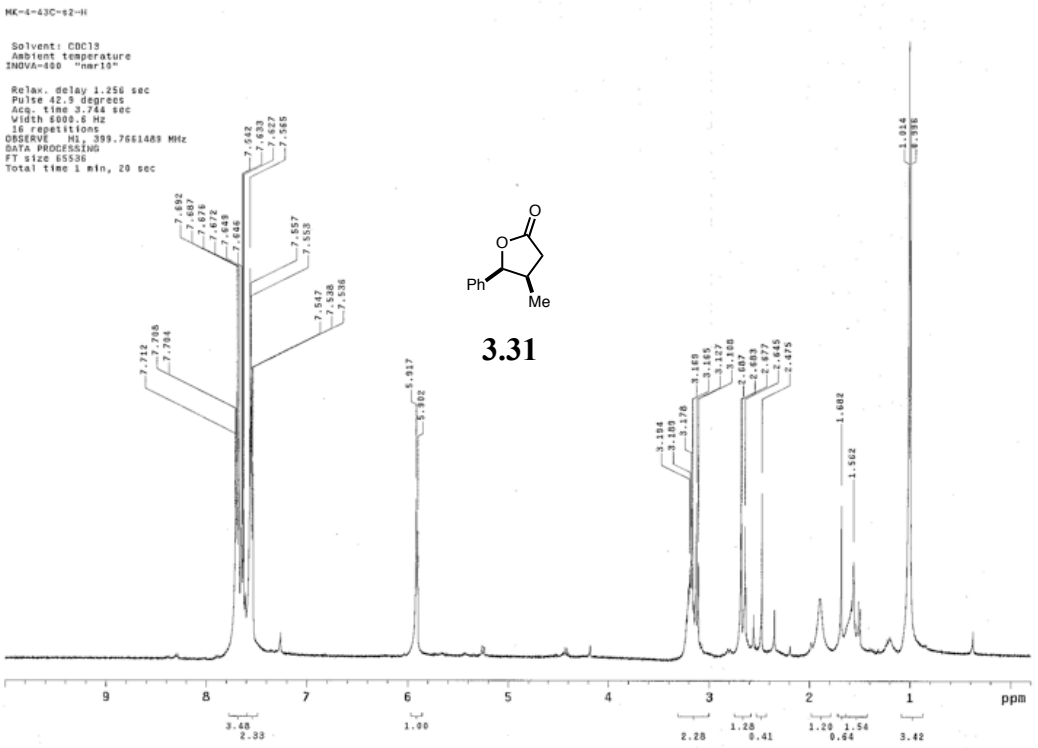

13C OBSERVE
MK-4-43B-s2-13C
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "nmr18"
Relax. delay 10.000 sec
Pulse 60.0 degrees
Acq. time 2.600 sec
Width 25000.0 Hz
428 repetitions
OBSERVE C13, 100.5212863 MHz
DECOUPLE H1, 399.7682755 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 209 hr, 8 min, 51 sec
Cy
Me
3.29
ppm

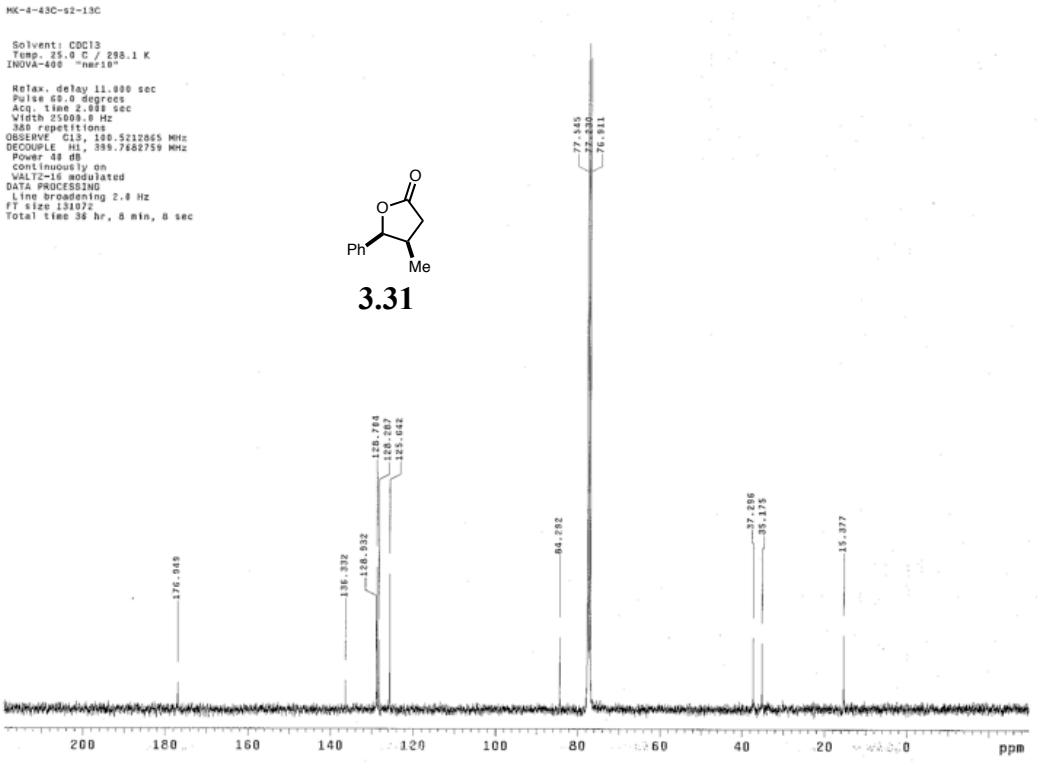


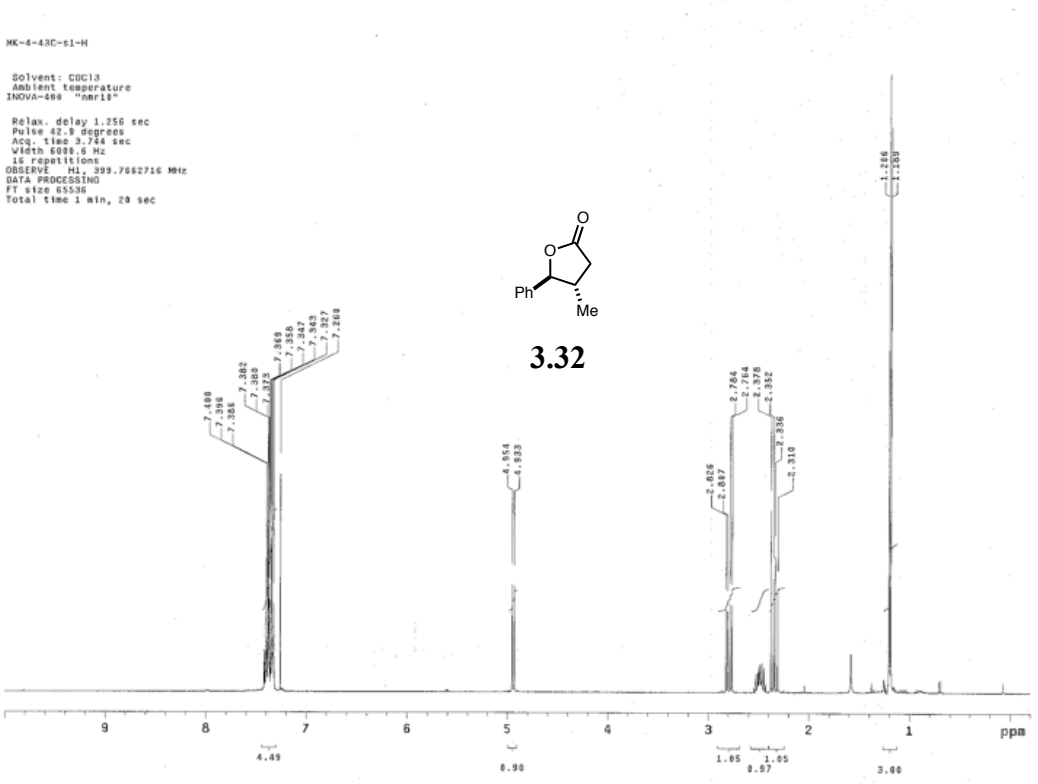
3.30

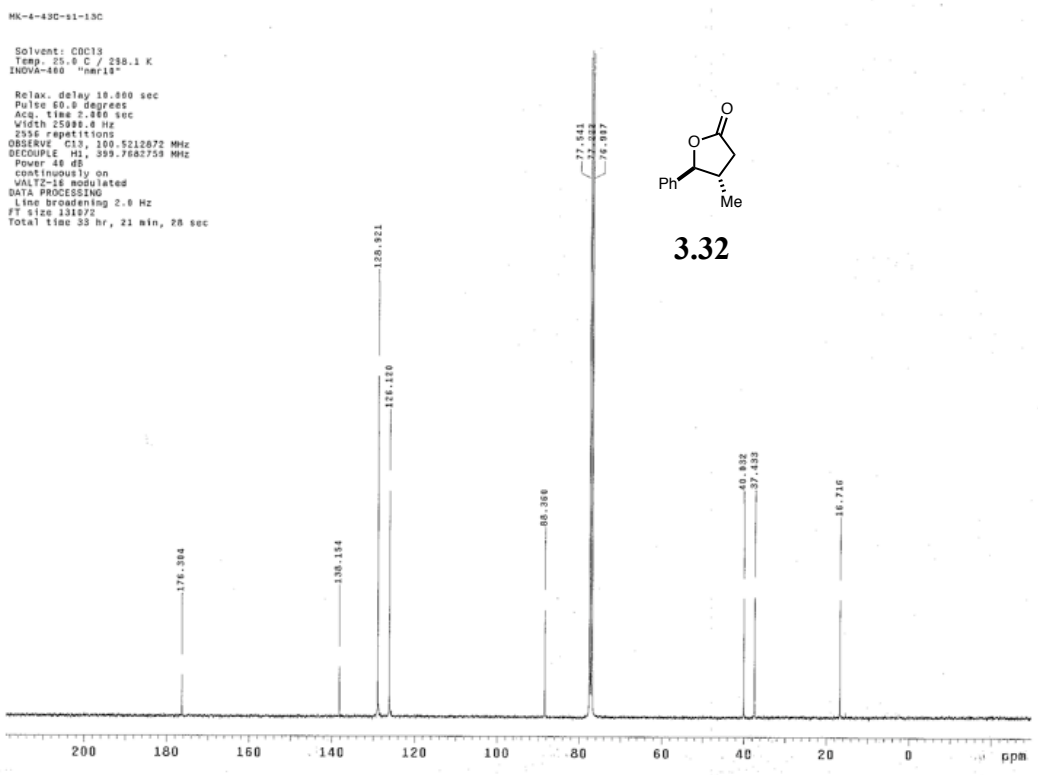


3.30

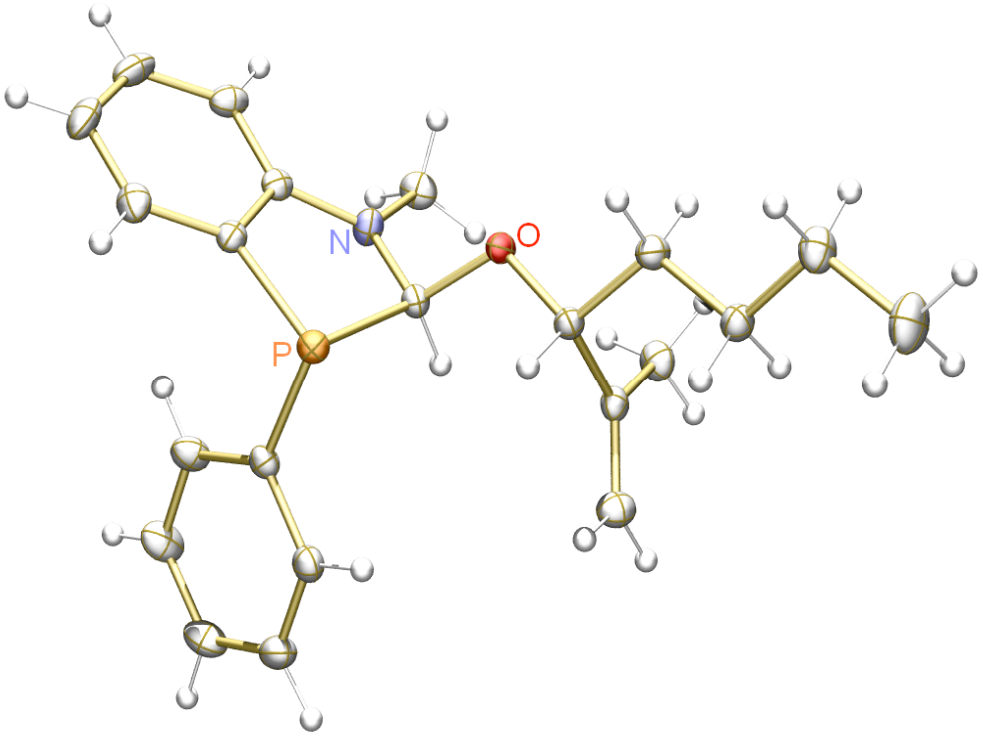

MK-4-43C-s2-H
Solvent: CDCl3
Ambient temperature
INOVA-400 "nmr10"
Relax. delay 1.256 sec
Pulse 42.3 degrees
Acq. time 3.744 sec
Width 6000.6 Hz
16 repetitions
OBSERVE H1, 399.7661489 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 20 sec
Ph
Me
3.31
ppm


MK-4-43C-s2-13C
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "nmr10"
Relax. delay 11.000 sec
Pulse 60.0 degrees
Acq. time 2.000 sec
Width 25000.0 Hz
380 repetitions
OBSERVE C13, 100.5212865 MHz
DECOUPLE H1, 399.7682759 MHz
Power 48 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 36 hr, 8 min, 8 sec
Ph
Me
3.31
ppm


MK-4-43C-s1-H
Solvent: CDCl3
Ambient temperature
INOVA-400 "nmr18"
Relax. delay 1.256 sec
Pulse 42.9 degrees
Acq. time 3.744 sec
Width 6008.6 Hz
16 repetitions
OBSERVE H1, 399.7662716 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 29 sec
Ph
Me
3.32
ppm


MK-4-43C-s1-13C
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "nmr18"
Relax. delay 10.000 sec
Pulse 60.0 degrees
Acq. time 2.000 sec
Width 25000.0 Hz
2556 repetitions
OBSERVE C13, 100.5212672 MHz
DECOUPLE H1, 399.7682759 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 33 hr, 21 min, 28 sec
Ph
Me
3.32
ppm

VI. X-ray Crystal Structure Data



The crystal structure of the above ligand has been deposited at the Cambridge Crystallographic Data Centre and has the deposition number: CCDC 752371.

Formula: C22 H28 N1 O1 P1

Unit cell parameters: a 7.383(3) b 12.365(5) c 12.416(5)
alpha 61.930(4) beta 84.607(5) gamma 83.628(5)
space group P-1